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RESIDUAL HEPATIC DAMAGE IN CATARRHAL JAUNDICE AS DETERMINED BY THE BILIRUBIN EXCRETION TEST

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Patients who have had catarrhal jaundice not infrequently manifest digestive complaints long after the attack of jaundice has subsided. The fact that on clinical investigation the patients present no detectable abnormalities has led to the impression that the symptoms are functional. An attempt to inquire whether residual hepatic damage rather than psychogenic factors may be responsible for these symptoms has led to this investigation.

By catarrhal or common infective hepatic jaundice is meant the condition as it is commonly understood and as it is described by Holt and Howland[1] and Rolleston and McNee.[2] It is a disease which is usually benign and probably caused by some unknown infection of the hepatobiliary system. It occurs sporadically or in epidemics independently of, or in association with, an acute infectious process. The anatomic features are not well known, since few cases which may safely be regarded as of this type come to necropsy. The condition is characterized clinically by gastro-intestinal symptoms, pyrexia and malaise and sometimes by mild prostration and abdominal pain. On examination, jaundice, an enlarged, tender liver, sometimes a palpable spleen, feces which may or may not appear acholic and bile pigments in the urine are noted. In addition, all of the other known causes of jaundice are eliminated. The duration of catarrhal jaundice usually varies from two weeks to two months. Not infrequently there are recurrences. A serious complication in rare instances is acute necrosis (yellow atrophy) of the liver.

MATERIAL AND METHOD

Material.—Cases in which a diagnosis of catarrhal jaundice had been made, in three instances within one year, and in eight instances within from three to

From the Department of Medicine, Chemical Division, and the Gastro-Intestinal Clinic, Johns Hopkins University and Hospital.

1. Holt, L. E., and Howland, John: Diseases of Infancy and Childhood, ed. 10, New York, D. Appleton and Company, 1933, p. 332.

2. Rolleston, Humphrey, and McNee, J. W.: Diseases of the Liver, Gall-Bladder and Bile Ducts, ed. 3, New York, The Macmillan Company, 1929, p. 596.

eighteen years prior to this study, were carefully selected from the records of the Johns Hopkins Hospital ward and outpatient departments. The records of the patients indicated that the clinical criteria outlined in the foregoing paragraph had been observed. Six patients (cases 2, 3, 4, 8, 9 and 10 in the table) presented no symptoms in the interval between the end of the acute illness and this study. The other five patients complained of weakness, lassitude, headache and vague digestive symptoms of a severity not sufficient to cause them to seek medical aid voluntarily.

Our series comprised eleven cases. A careful history was obtained from each patient, and a complete physical examination was made, including studies of the urine, stool and blood. In the cases in which the procedures were possible, cholecystography (with orally administered dye) and duodenal drainage were done

Data on Eleven Patients with Catarrhal Jaundice of Varying Duration

Case	Age of Patient	Duration of Jaundice	Interval Between Jaundice and Test, Years	Results of Physical Examination*	Results of Cholecystography	Results of Duodenal Drainage	Van den Bergh Reaction	Bilirubin Retention, per Cent
1	27	2 weeks, ambulatory	7	Essentially negative	Normal	Negative	Negative	11.3
2	9	3 weeks, ambulatory	3	Essentially negative	.....	.....	Faint indirect trace	0.0
3	53	11 days, ambulatory	1/6	Essentially negative	Normal	Negative	Negative	10.7
4	25	7 days, ambulatory	1	Essentially negative	Normal	Negative	Indirect trace	16.2
5	22	15 days, ambulatory	3	Essentially negative	Normal	Negative	Indirect trace	39.5
6	16	2 weeks, ambulatory	8	Underweight, secondary anemia	Subnormal concentration of dye	.....	Indirect trace	50.0
7	16	10 days, ambulatory	5	Secondary anemia	Normal	.....	Faint indirect trace	22.0
8	40	6 weeks, hospitalized	18	Not done	.....	Negative	Negative	19.0
9	33	4 weeks, hospitalized	8	Essentially negative	.....	.....	Negative	0.0
10	42	4 weeks, hospitalized	1/4	Essentially negative	Normal	Negative	Faint indirect trace	22.1
11	23	.....	3	Essentially negative	Normal	Negative	Negative	16.7

* Performed at the time that the bilirubin test was made.

to determine if disease of the gallbladder existed. The van den Bergh reaction and the bilirubin excretion test were then performed.

The commonly used tests of hepatic function are mainly of three types: (1) those, such as the van den Bergh reaction, used to detect the retention of bile pigments in the blood; (2) those depending on the ability of the liver to excrete dyes, such as bromsulphalein, bengal rose and phenol-tetra-chlor-phthalein when introduced intravenously, and (3) those determining the metabolic activity of the liver cells, such as the levulose and galactose tolerance tests.

The van den Bergh test was used in this study for comparative purposes. The aforementioned dye tests were not employed, since they are of relatively little value except when gross hepatic changes are present. The galactose tolerance test is of value only in the differential diagnosis of jaundice. Our cases were free from icterus. The same objection holds for the levulose tolerance test as for the dye

tests of hepatic function. The results are positive only when extensive hepatic damage has occurred. Incidentally, Kimball,[3] in an excellent study of the levulose tolerance test, did not use it in cases of catarrhal jaundice.

We employed, therefore, the excretion of intravenously injected bilirubin, originally described by Eilbott and von Bergmann,[4] as a means of determining the hepatic function in our cases. The work of these authors, as well as that of Harrop and Barron[5] and our own work,[6] has led us to the conclusion that this is one of the most sensitive methods of determining the state of hepatic function.

Method.—The method of determining the existence of hepatic involvement by the excretion of intravenously injected bilirubin, together with certain modifications that one of us (L. J. S.[6]) has introduced and which are now employed as a routine in the medical clinic of this hospital, has been described in detail previously. The test, briefly, is performed as follows: A total amount of bilirubin equal to 1 mg. per kilogram of body weight is dissolved in 15 cc. of one-tenth molar solution of sodium carbonate which has been previously brought to the boiling point and then allowed to cool to 80 C. The bilirubin dissolves completely, and a clear iodine-colored solution is obtained. A control sample of oxalated blood is collected in a dry syringe to prevent hemolysis, and with the needle in situ the bilirubin is then injected intravenously. Oxalated samples of blood are obtained from the other arm within five minutes and again four hours after the injection. In the past three years nearly one hundred bilirubin tests have been performed in our clinic, and in no instance have we observed uncomfortable reactions. The concentration of bilirubin in the plasma is determined by means of the Ernst and Förster method.[7] The plasma is precipitated by redistilled acetone, which is used in different concentrations, depending on the amount of bilirubin in the sample. Thus, with the control and with the samples taken after four hours, 2 cc. of acetone is added to 2 cc. of plasma, while with 1 cc. of the plasma of the specimen taken after five minutes 4 cc. of acetone is used. After the plasma and acetone mixtures are shaken, the samples are centrifugated and filtered directly into a clean, dry colorimeter cup and compared with a standard solution of 1:6,000 potassium dichromate in distilled water. Except during the actual reading in the colorimeter, the acetone solutions of bilirubin must be protected from the light. The bilirubin content of the specimen taken five minutes after the injection minus the bilirubin content of the control sample is considered to contain 100 per cent of the injected pigment. The percentage of bilirubin retained in the sample taken

3. Kimball, Stockton: The Levulose Tolerance Test; a Study of Its Value with Special Reference to Mild and Chronic Diseases of the Liver, Guy's Hosp. Rep. **82**:157 (April) 1932.

4. Eilbott, W.: Funktionsprüfung der Leber mittles Bilirubinbelastung, Ztschr. f. klin. Med. **106**:529, 1927. von Bergmann, G.: Zur funktionellen Pathologie der Leber insbesondere der Alkohol-Aetiologie der Cirrhose, Klin. Wchnschr. **6**: 776, 1927.

5. Harrop, G. A., Jr., and Barron, E. S. G.: The Excretion of Intravenously Injected Bilirubin as a Test of Liver Function, J. Clin. Investigation **9**:577, 1931.

6. Soffer, L. J.: Bilirubin Excretion as a Test of Liver Function During Normal Pregnancy, Bull. Johns Hopkins Hosp. **52**:365 (May) 1933.

7. Ernst, Z., and Förster, J.: Ueber die Bestimmung des Blutbilirubins, Klin. Wchnschr. **3**:2386, 1924.

after four hours is then calculated, after previous subtraction of the bilirubin contained in the control. The following formulas are employed to determine the amount of bilirubin in the various samples:

$$\text{Control and four hour specimens} = 0.329 \times 2 \text{ (dilution)} \times \frac{\text{reading of standard}}{\text{reading of unknown}}$$

$$\text{Five minute specimen} = 0.329 \times 5 \text{ (dilution)} \times \frac{\text{reading of standard}}{\text{reading of unknown}}$$

On the basis of previously published control studies [6] of normal persons, retention of more than 5 per cent of the injected pigment after four hours is considered pathologic.

RESULTS

The results are assembled in the accompanying table. The various examinations other than the tests of hepatic function gave essentially negative results in all instances. In nine of the eleven cases, however, there was a distinctly abnormal response to the bilirubin test. At the time of the study, in four of the nine cases (3, 4, 8 and 10) the patients were symptomless; the remaining five patients complained of indefinite digestive disturbances.

The experience of one of us (Dr. Soffer [6]) with this test in normal control subjects and in patients evidencing conditions in which the liver was not involved coincided with the results of other investigators,[4] rendering the inclusion of our detailed data on this point unnecessary.

Attention is directed to the degree of retention of bilirubin which indicates residual hepatic involvement in these cases. In nine of the eleven patients, all of whom were regarded as having completely recovered from catarrhal jaundice, the degree of retention of the injected pigment varied from 10.7 to 50 per cent. In six of the nine cases the original attack of jaundice occurred within from three to eighteen years prior to this study. These results are in line with Kalk's [8] experience, the publication of which appeared while this work was in progress.

COMMENT

Catarrhal or common infective hepatic jaundice has usually been regarded as an innocuous process, since the clinical course in many instances is relatively short and not severe. The apparent well-being of the patient as well as the lack of objective evidence indicating residual hepatic involvement after the jaundice has subsided has served to promote this impression.

The delay in the excretion of intravenously injected bilirubin is, in our opinion, as already noted, one of the most sensitive of present-day means of determining hepatic damage. The fact that such abnormal results were secured in nine of eleven cases in which the attacks of

8. Kalk, Heinz: Klinische Untersuchungen über die Frage des latenten Leberschadens, Deutsche med. Wchnschr. **58**:1078 (July 8); 1119 (July 15), and 1160 (July 22) 1932.

jaundice occurred from months to many years previous to the study suggests not only that the process is more serious than it is generally regarded but that the hepatic disturbance is in all probability permanent.

Thus, these data give rise to another concept of the disease. Instead of two groups, one in which the hepatobiliary involvement is thought to have completely subsided without residue and a smaller group of rarer cases in which the condition progresses to acute necroses, we now have a third group, which is possibly the largest, in which the chief objective manifestation of the disease is an abnormal delay in the excretion of the injected pigment after four hours. It is conceivable that a number of patients in this group may eventually acquire further hepatic disease, such as cirrhosis.

As will be noted in the table, the severity of an attack bears no relation to the degree of residual hepatic involvement, as determined by this test. This appears to be true with respect to the presence or absence of persisting symptoms and the extent of impaired hepatic function. For instance, the patient in case 4 was symptomless; a friend directed his attention to the yellow discoloration of his eyes. A year later, when the patient was still symptomless and apparently well, the bilirubin retention measured 16.2 per cent. The patients in cases 3 and 8 were symptomless when studied, yet the bilirubin retentions were 10.7 and 19 per cent. The patients in cases 2 and 9, who presented no retention of bilirubin, were asymptomatic. The remaining patients, as already indicated, complained of indefinite discomforts.

SUMMARY

Eleven patients who had had catarrhal jaundice within from three months to eighteen years prior to the investigation were studied by means of the bilirubin excretion test for evidence of residual hepatic damage. It must be emphasized that the original attack was free from such complications as acute yellow atrophy of the liver. Nine of the eleven patients showed degrees of retention of the injected pigment that varied from 10.7 to 50 per cent. Six of the nine patients had had catarrhal jaundice within from three to eighteen years before the investigation.

The degree of residual hepatic damage apparently bears no relationship to the severity of the attack. In view of the response to the test in these cases it is concluded that catarrhal jaundice is not innocuous as is commonly believed, since in a good many instances an impairment of hepatic function occurs which is permanent.

NOTE.—The following inadvertent omission has come to our attention: Jankelson and Gargill (Bilirubin Liver Function Test, New England J. Med. **204**:547 [March 12] 1931) reported that in chronic cholecystitis the percentages of bilirubin retention were within normal limits.

FACTORS INVOLVED IN THE PRODUCTION OF SKELETAL MUSCLE PAIN

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The cause of muscular pain and the various factors that influence it have been a subject of controversy for many years. Lewis, who has investigated the subject extensively has presented an excellent review of the pertinent literature.[1] More recently Kissin [2] reviewed the subject from a different angle. While it is now generally accepted that ischemia is the cause of muscular pain, such as occurs in angina pectoris and intermittent claudication, the immediate factors responsible for the pain have not been fully established. The pain which develops in contracting muscles during ischemia might be caused (1) by the direct or indirect action of the lack of oxygen which accompanies ischemia, (2) by the diminution of other materials normally supplied by the arterial blood, (3) by the incomplete mechanical removal of products of muscular metabolism which follows the retardation of the blood flow or (4) by the combined action of several of these factors. Recently, Kissin,[2] working in this laboratory, showed that generalized anoxemia without ischemia can lead to the development of pain in an exercising muscle. His study, however, did not preclude the possibility that the other factors mentioned which accompany ischemia might also play a significant rôle in the production of pain. The present report deals with the latter problem.

METHOD

The evaluation of the action of the various factors was based on observations obtained during and following exercise under a variety of conditions in a group of ten normal young subjects. Some of the experiments reported in this study are a repetition of those reported by

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Aided by the Frederick K. Babson Fund of the Michael Reese Hospital.

From the Heart Station and the Cardiovascular Laboratory, Department of Physiology, Michael Reese Hospital.

1. Lewis, T.: Pain in Muscular Ischemia; Its Relation to Anginal Pain, Arch. Int. Med. **49**:713 (May) 1932.

2. Kissin, M.: The Production of Pain in Exercising Skeletal Muscle During Induced Anoxemia, J. Clin. Investigation **13**:37 (Jan.) 1934.

other observers, notably by Lewis, Pickering and Rothschild [3] and by Kissin; [2] others are new. Most of our observations were made on the leg, whereas previous workers studied the arm.

The arm exercise, unless otherwise stated, consisted of clenching one hand sixty times per minute, in time with a metronome, using maximal effort. During this exercise the subject sat at ease in a chair with the exercising arm supported horizontally on a rest. The leg exercise, unless otherwise stated, consisted of extending one foot against a load sixty times per minute in time with a metronome. The apparatus was arranged to permit the extending foot to lift a weight of 500 Gm. through a distance of 15 cm. This exercise did not require maximal effort. During the exercise the subject reclined on a cot with the lower extremities supported in a horizontal position. A preliminary period of rest of at least ten minutes preceded each period of exercise, unless otherwise stated. Lewis, Pickering and Rothschild [3] found that this interval was sufficient to permit full recovery from previous activity.

Complete ischemia was produced in these experiments with a sphygmomanometer cuff inflated to a pressure considerably above the systolic blood pressure. In experiments on the forearm the pressure in the cuff, which was placed on the upper arm, was raised to about 170 mm. of mercury; in the experiments on the leg the pressure in the cuff, which was placed on the lower part of the thigh, was raised to about 200 mm. of mercury.

Circulatory stasis without complete ischemia was produced in these experiments by maintaining a pressure of 80 mm. of mercury in the cuff, a pressure definitely below the systolic and approximately at the level of the diastolic blood pressure of the subjects. The obstruction of the venous outflow produced in this way leads to the accumulation of blood in the limb, and, for a limited time, oxygen is available for the tissues, namely, the oxygen contained in the congested capillaries. The supply of oxygen available to the tissues following venous obstruction is greater than in complete ischemia, since the volume of blood retained in the limb is greater in the former condition and the circulation is not completely stopped. However, the supply of oxygen following venous obstruction is less than normal because of the circulatory stagnation which is produced in the limb.

Various degrees of generalized anoxemia were produced in these experiments by having the subject breathe from a Tissot spirometer containing various mixtures of gases at different times.[2] The oxygen content of samples of inspired air was determined with the Haldane apparatus.

3. Lewis, T.; Pickering, G. W., and Rothschild, P.: Observations upon Muscular Pain in Intermittent Claudication, Heart **15**:359, 1931.

OBSERVATIONS

The observations consisted primarily in determining the time and circumstances under which continuous pain, as described by Lewis,

TABLE 1.—*Effect of a Preliminary Period of Complete Ischemia on the Time of Appearance of Pain During Exercise of the Lower Extremity*

	Pain Produced by		Time When Pain Appeared		Time When Pain Became Unbearable	
Subject	Ischemia for 10 Minutes	Exercise for 10 Minutes	Exercise and Ischemia Started at the Same Time, Sec.	Exercise Started 10 Minutes After Ischemia, Sec.	Exercise and Ischemia Started at the Same Time, Sec.	Exercise Started 10 Minutes After Ischemia, Sec.
P. M.	No	No	45 48	23	80 80	33
S. P.	No	No	61	14	103	63
J. P.	No	No	60	15	94	74
B. W.	No	No	148	48	224	138
H. B.	No	No	78	56	130	103
K. J.	No	No	69	45	103	84
R. F.	No	No	80	76	200	141
J. S.	No	No	78	88	183	119
H. K.	No	No	139	126	175	154
L. W.	No	No	85	28	147	85
R. F.*.....	No	No	148	106	238	198

* In this test exercise was at the rate of thirty movements per minute.

TABLE 2.—*Effect of a Preliminary Period of Complete Ischemia on the Time of Appearance of Pain During Exercise of the Upper Extremity*

	Pain Produced by		Time When Pain Appeared		Time When Pain Became Unbearable	
Subject	Ischemia for 5 Minutes	Exercise for 5 Minutes	Exercise and Ischemia Started at the Same Time, Sec.	Exercise Started 5 Minutes After Ischemia, Sec.	Exercise and Ischemia Started at the Same Time, Sec.	Exercise Started 5 Minutes After Ischemia, Sec.
P. M.	No	No	43 38	12	65 60	38
S. P.	No	No	28 42	8	73 80	22
J. P.	No	No	55	30	70	65
B. W.	No	...	31	20	50	51
H. B.	No	...	39	30	60	50
K. J.	No	...	48	32	70	62
R. F.	No	...	65	43	101	70
J. S.	No	...	64	52	95	65
H. K.	No	...	60	50	80	76
L. W.	No	...	31	16	69	60
R. F.*.....	No	No	58	68	90	100

* In this test exercise was at the rate of thirty movements per minute.

Pickering and Rothschild,[3] developed and the time and circumstances under which it disappeared.

It will be seen from the data summarized in tables 1 and 2 for both the leg and the arm that while complete ischemia without exercise, or the

reverse, did not lead to pain, the combination of the two did. This has already been shown by Lewis, Pickering and Rothschild.[3] However, contrary to the results of these workers, we found that when the complete ischemia was started five or ten minutes before the exercise, the time required for the onset of mild and unbearable pain was considerably

TABLE 3.—*Effect of Continuing Complete Ischemia on Appearance of Pain When Exercise Is Stopped Before Pain Develops*

Procedure	Control Exercise and Ischemia Started Simultaneously, Sec.	Ischemia Continuous, but Exercise Stopped After			Subject
		30 Sec.	26 Sec.	16 Sec.	
Onset of pain after start of ischemia	35 30	181	130	210 190	P. M. (upper extremity)
Pain became unbearable after start of ischemia	52 45	200	185	610 625	
		28 Sec.	17 Sec.		
Onset of pain after start of ischemia	31 32	130 140	320 340		S. P. (upper extremity)
Pain became unbearable after start of ischemia	55 62	349 354	*		
		35 Sec.			
Onset of pain after start of ischemia	39 42	285 260			B. W. (upper extremity)
Pain became unbearable after start of ischemia	69 63	*			
		75 Sec.			
Onset of pain after start of ischemia	80 100	512			R. F. (upper extremity)
Pain became unbearable after start of ischemia	100 125	*			
		40 Sec.			
Onset of pain after start of ischemia	45	185			P. M. (lower extremity)
Pain became unbearable after start of ischemia	85	*			
		40 Sec.			
Onset of pain after start of ischemia	43	301			S. P. (lower extremity)
Pain became unbearable after start of ischemia	107	*			

* Pain increased but did not become unbearable.

shortened in practically all our experiments. In the leg the abbreviation of the two intervals was marked in most instances.

The action of complete ischemia in the production of pain in the arm was shown on repeating another type of experiment of Lewis and his co-workers,[3] which consisted in stopping the exercise short of the point at which pain would have appeared, the ischemia being maintained. The results summarized in table 3 show that in our experiments continuation of the ischemia after stopping the exercise led to the development of pain, contrary to the findings of Lewis and his co-workers. The time of its appearance was considerably delayed, in many instances

beyond five minutes. In some experiments the pain did not increase sufficiently to become unbearable during the fifteen to twenty minute period of ischemia after the cessation of exercise. Ischemia was not continued longer than this because numbness and tingling became noticeable. The interval before the onset of pain was least when the end of the period of exercise was closest to the time at which pain appeared in the preliminary experiments. When the exercise was stopped earlier, the delayed pain often started so insidiously that the exact time of its onset was not always sharply defined, the subject being able to state only that the pain had begun in the previous thirty to sixty seconds.

TABLE 4.—*Effect of Generalized Anoxemia and Circulatory Stasis on Appearance of Pain During Exercise of the Lower Extremity (Subject S. P.)*

Test Done		Stasis Present or Absent	Oxygen Level in Inspired Air,* Volume per Cent	Pain Appearing After Onset of Exercise, Time in Seconds	Pain Becoming Unbearable After Onset of Exercise, Time in Seconds
Day	Order				
6	15	No	21.0	No pain in 600 seconds	
1	1	No	14.5	No pain in 600 seconds	
1	3	No	13.6	No pain in 600 seconds	
2	4	No	11.2	No pain in 540 seconds	
3	7	No	10.1	No pain in 480 seconds	
4	10	No	7.6	No pain in 720 seconds	
6	14	Yes	21.0	No pain in 600 seconds	
1	2	Yes	15.4	No pain in 600 seconds	
4	11	Yes	14.8	332	964
4	9	Yes	14.1	338	756
2	5	Yes	11.8	219	793
3	6	Yes	10.8	195	630
3	8	Yes	9.3	158	382
5	12	Yes	8.1	54	168
6	13	Ischemia present (control)	21.0	34	86

* In all cases the exercise was begun two minutes after anoxemia was started.

In the only subject tested generalized anoxemia alone did not lead to the development of pain when the lower limb was exercised for ten minutes (in the same way as in the complete experiments on ischemia), even when the level for oxygen in the inspired air was as low as 7.6 per cent by volume (table 4). Pain did appear, however, and become unbearable when the generalized anoxemia was associated with circulatory stasis. As shown in table 4, the pain appeared when the oxygen content of the inspired air was reduced to 14.8 per cent by volume. The periods of exercise necessary to cause pain and to make it unbearable shortened progressively as the degree of generalized anoxemia was increased. These intervals of time, however, were longer than in complete ischemia, even when the level for oxygen in the inspired air was 8.1 per cent by volume (table 4). The interval between the first appearance of pain and the time when it became unbearable also shortened as the degree of anoxemia was increased.

The rôle of circulatory stasis was shown in another group of experiments on the leg, in which the periods of exercise required for pain to appear and to become unbearable were determined in a preliminary period of exercise under total ischemia; these intervals of time were compared with those of a second period of exercise and ischemia carried out after a short interval during which the total ischemia was temporarily abated and one of the following four conditions was substituted: (1) circulatory stasis and exercise, (2) exercise alone, (3) circulatory stasis alone, (4) a state of rest, with no stasis or exercise. The results are summarized in table 5.[4] When the interval between the two ischemic periods was short, as in L. W., the pain appeared sooner in the second period than in the first, regardless of whether or not exercise or stasis

TABLE 5.—*Effect of Temporary Relief of Ischemia on the Time Pain Reappears During a Second Ischemic Period (Lower Extremity)*

	Onset of Pain					Pain Becoming Unbearable					
		Second Period of Exercise and Ischemia After Interlude with					Second Period of Exercise and Ischemia After Interlude with				
Subject	First Period of Exercise and Ischemia, Sec.	Stasis and Exercise, Sec.	Stasis Alone, Sec.	Exercise Alone, Sec.	No Stasis or Exercise, Sec.	First Period of Exercise and Ischemia, Sec.	Stasis and Exercise, Sec.	Stasis Alone, Sec.	Exercise Alone, Sec.	No Stasis or Exercise, Sec.	Duration of Interlude, Sec.
S. P.	65 ± 15	27	23	50	80	127 ± 15	71	71	113	155	185
P. M.	44 ± 8	27	46	40	45	78 ± 12	55	62	69	71	150
R. F.	94 ± 20	35	69	23	126	158 ± 25	105	134	45	176	180
L. W.	75 ± 5	40	23	13	46	125 ± 18	85	67	46	98	45

was present during the interval between them. When a longer period of rest was allowed between the two ischemic periods the onset of mild and unbearable pain did not occur earlier in the second period of exercise and ischemia than in the first. However, when the exercise, the stasis or both were maintained during this longer interval, mild and unbearable pain appeared earlier in the second period of exercise and ischemia than in the first. In the case of S. P. a decrease of these intervals of time in the second period of ischemia and exercise occurred when stasis was continued in the interlude; maintaining exercise alone during the interlude had no such effect. In the case of R. F., however, the reverse was true; and in the case of P. M. this abbreviation in the second period of ischemia and exercise occurred only when both the exercise and the stasis were maintained in the interlude.

4. In this group of experiments the control is the average of four determinations. It will be seen that the intervals of time required for the development of mild and unbearable pain are more variable than those reported by Lewis, Pickering and Rothschild [8] and those found in our other determinations.

In S. P., after unbearable pain had developed while exercising during general anoxemia and circulatory stasis, a short interval of rest, without abating the general anoxemia and circulatory stasis, was followed in every trial by a shortening of the intervals required to produce mild or unbearable pain in the second period of exercise, as the results assembled in table 6 show.[5] In this subject a similar period of rest, without anoxemia or stasis, was not followed by such an abbreviation of the

TABLE 6.—*Effect of Temporary Interlude of Rest with Generalized Anoxemia and Circulatory Stasis Maintained on the Time Pain Reappears (Lower Extremity, Subject S. P.)*

Onset of pain				
First period of exercise, seconds	332	219	195	158
Second period of exercise, seconds	223	70	28	136
Time at which pain became unbearable				
First period of exercise, seconds	964	793	630	382
Second period of exercise, seconds	425	170	119	284
Oxygen in inspired air, per cent by volume				
First period of exercise	14.1	11.8	10.8	9.3
Second period of exercise	13.8	16.3	7.9	8.5
Duration of interlude, seconds	150		250	

TABLE 7.—*Effect of Ischemia, Stasis and Generalized Anoxemia on the Disappearance of Pain Produced by Exercise of the Lower Extremity*

Subject	Ischemia Relieved, Exercise Stopped, No Stasis, Seconds	Ischemia Relieved, Exercise Persists, No Stasis, Seconds	Ischemia Relieved, Exercise Stopped, Stasis Persists, Seconds	Ischemia Relieved, Exercise and Stasis Persist, Seconds	Ischemia Persists, Exercise Stopped	Generalized Anoxemia and Stasis Persist, Exercise Stopped, Seconds	Generalized Anoxemia and Exercise Persist, Stasis Relieved, Seconds
S. P.	5 to 7	10 to 14	14	13	Pain does not disappear, but continues unabated or even increases	149 (16.3%)* 146 (14.1%)* 116 (9.2%)* 241 (7.9%)*	4 (16.3%)* 38 (8.9%)* 54 (8.1%)*
P. M.	5 to 10	4	10	10			
R. F.	5 to 19	7	4 to 15				
L. W.	6 to 22	10	5 to 31	5			

* Oxygen level in the inspired air, per cent by volume.

second period of exercise even though the exercise was carried out during complete ischemia (table 5).

The time required for pain to disappear under various conditions was also analyzed, and the data on four subjects are assembled in table 7. No essential difference was found in the time taken for pain to disappear, provided the complete ischemia was relieved, regardless of whether or not circulatory stasis or exercise was continued. On the other hand, so long

5. The more marked shortening in the third trial (third column of table 6) is due in part to the lowered oxygen content in the inspired air when the second period of exercise was carried out, which followed the necessarily rapid refilling of the spirometer in the interval between periods of exercise.

as the ischemia was maintained pain was found to persist unabated or even to increase after the exercise was stopped.[6] Furthermore, the time taken for pain to disappear was found to be prolonged when generalized anoxemia and circulatory stasis were maintained after the cessation of exercise. The time taken for pain to disappear, however, was prolonged only slightly if exercise and general anoxemia were maintained but circulatory stasis was relieved.

COMMENT

Our results, with the few exceptions to be discussed later, are in accordance with the observations of Zak,[7] MacWilliam and Webster,[8] Lewis, Pickering and Rothschild,[3] Reid [9] and Kissin.[2]

They confirm previous observations that continuous pain is brought on after a short interval (from one to two minutes) in the exercising muscle when complete ischemia is produced, and that the pain becomes unbearable if exercise is continued. However, our results show that exercise with circulatory stasis but without anoxemia fails to produce pain in the leg in ten minutes under the conditions of our experiments, although in one subject (S. P.) on one occasion exercise with circulatory stasis led to the development of pain after sixteen minutes and ten seconds, just before tingling began. The pain produced by exercise of both the arm and the leg during complete ischemia disappears after a short lag whenever the complete ischemia is relieved, even if the exercise is continued and circulatory stasis is maintained (table 7). These observations seem to indicate that anoxemia must be severe to become an important element in the production of pain in an exercising muscle during ischemia (Kissin [2]).

In our experiments general anoxemia alone, however, failed to produce pain in ten minutes in the exercising muscles of the leg unless associated with circulatory stasis (table 4). This apparent contradiction of Kissin's observations probably depends on the different type of exercise used in the two investigations. Extension of the foot at the ankle, which was carried out in the present study, is a movement constantly employed in walking, so that training may tend to make compen-

6. While the exercise was continued until the pain became unbearable and forced the subject to stop the exercise, nevertheless in some, pain became even more marked after the exercise had ceased but while the ischemia was maintained.

7. Zak, E.: Ueber den Gefässkrampf bei intermittierendem Hinken und über gewisse Kapillomotorische Erscheinungen, Wien. Arch. f. inn. Med. **2**:404, 1921.

8. MacWilliam, J. A., and Webster, W. J.: Some Applications of Physiology to Medicine: I. Sensory Phenomena Associated with Defective Blood Supply to Working Muscles, Brit. M. J. **1**:51, 1923.

9. Reid, C.: Experimental Ischemia: Sensory Phenomena, Fibrillary Twitchings, and Effects on Pulse, Respiration, and Blood-Pressure, Quart. J. Exper. Physiol. **21**:243, 1931.

satory adjustment easier than in the less constantly employed gripping movement of the hand used by Kissin. The conditions of the leg exercise could not conveniently be made more strenuous. It is not easy to perform the leg exercise faster than sixty times a minute, nor is it convenient to load the exercising leg with weights approaching those lifted by the foot in walking. Furthermore, the degree of general anoxemia that can be employed is set by the general reaction of the subject. Our observations, however, serve to emphasize the fact that circulatory stasis is an important factor in the production of pain during ischemia. Circulatory stasis can be considered as acting to supplement the action of anoxemia. The important rôle of stasis is also seen in the experiments assembled in tables 5 and 6, in which it is shown that the presence of stasis in the interval between the first and second periods of exercise and ischemia (also the periods of exercise and anoxemia) had a definite tendency to abbreviate the time of onset of mild and of unbearable pain.

It appears, therefore, that both stasis and anoxemia are important in determining the appearance of pain during exercise. They also have an important influence on the disappearance of pain. When both stasis and anoxemia are maintained, pain abates more slowly than when they are relieved (table 7). If the anoxemia and stasis are at a maximum, as in complete ischemia, pain continues unabated after the cessation of the exercise. Anoxemia has a greater effect in prolonging pain than stasis has, since without stopping the exercise, relieving the latter but continuing the former prolongs the time before pain disappears, whereas the relief of the former but not of the latter has little effect in prolonging the time before pain disappears (table 7).

A repetition of some of the experiments of Lewis, Pickering and Rothschild [3] with complete ischemia yielded results different from those which they obtained. We found that a preliminary period of ischemia definitely shortens the duration of exercise necessary to produce mild and unbearable pain in both the arm and the leg (tables 1 and 2). Lewis and his co-workers reported that a preliminary period of ischemia had no such effect in the arm. Furthermore, we found that continuing the ischemia after stopping the exercise short of the point at which pain appears led to the development of pain in the arm (table 3), whereas Lewis and his co-workers reported that under such circumstances pain did not develop. If our results are correct, there is no necessity to assume, as Lewis has done, that the stimulated pain nerve endings are in the tissues surrounding the muscle and not in the muscles themselves.

Our results suggest that the only difference between the metabolism of rest and that of exercise is one of degree. A rough calculation would place the ratio between the two somewhere close to 1 : 20 to 1 : 80 in our experiments, which is the magnitude generally accepted on the basis

of thermodynamic studies (Hill [10]). Our observations are in accord with the finding of Lewis and his co-workers [3] that exercise without ischemia followed immediately by ischemia without exercise leads to pain, a result which appears paradoxical in view of the other results reported by them. We interpret this observation of theirs as follows: The preliminary period of exercise built up the concentration of the pain-producing substance which was augmented by the metabolism of the resting ischemic limb sufficiently to raise the pain-producing substance above the threshold for pain. The hypothesis of diffusion of the pain-producing substance which Lewis used to explain his results is, as our observations show, at present unnecessary. In view of our findings, the pain-producing substance could act just as readily within the muscle.

Our results further incline us to the view held by previous observers that the pain-producing factor is a chemical substance. However, our results indicate that this is formed during muscular metabolism, not only during exercise but also while the muscle is at rest. The rate of formation is slow while the muscle is at rest but is greatly accelerated during exercise. This substance is diffusible into the blood stream and can be carried away, but it can also be changed locally, in the presence of an adequate amount of oxygen, into substances which do not cause pain. Interference with either its mechanical removal by the circulation or its local oxidation, or both, will lead to the accumulation of the pain-producing substance in the muscles. If the interference with these two factors is sufficiently great in relation to the muscular activity of the part, then the concentration of the pain-producing substance can become great enough to exceed the threshold necessary to stimulate the pain nerve endings.

Our experiments do not rule out the possibility that the threshold of the pain nerve endings may be variable. Thus it is not at all unlikely that one of the actions of ischemia, circulatory stasis, anoxemia or exercise itself might be to enhance the susceptibility of the pain nerve end-organs to the pain-producing substance, thus lowering the threshold to pain. It is known (Lewis and co-workers [11]) that ischemia continued for forty minutes has the reverse action; namely, it deadens sensations of pain in the ischemic limb.[12]

10. Hill, A. V.: Muscular Movement in Man, New York, McGraw-Hill Book Company, Inc., 1927.

11. Lewis, T.; Pickering, G. W., and Rothschild, P.: Centripetal Paralysis Arising Out of Arrested Bloodflow to the Limb, Including Notes on a Form of Tingling, Heart **16**:1, 1931.

12. The variability in the amount of exercise necessary to lead to mild and to unbearable pain, which amounted to from ten to twenty seconds from day to day, may be due in part to a variability in the sensitivity of the pain nerve endings.

Our results show clearly that there is a prepain stage in which the pain-producing substance is above normal but below the pain-producing threshold. It follows, therefore, that the absence of pain, or its disappearance, does not imply full restoration of the muscle to normal as far as the pain-producing substance is concerned, but merely indicates a sufficient diminution in the amount of the pain-producing substance to reduce its concentration below the threshold for pain. This is shown strikingly by the variability of the duration of exercise necessary to produce mild and unbearable pain after different preliminary conditions. As indicated by our results improvement in the condition of the muscle, in the sense of delaying pain on exertion, would be attainable by decreasing the work of the muscle, or its tone, by increasing the supply of oxygen and by improving the circulation locally.

This analysis may be applicable to the mechanism for the production of pain in intermittent claudication and angina pectoris.

SUMMARY

Our results show that the immediate cause of continuous muscular pain, such as occurs when an ischemic muscle is exercised, is not produced by a single mechanism but that muscular activity, anoxemia, circulatory stasis and possibly other processes contribute to its production.

BLOOD CHOLESTEROL AND HYPOMETABOLISM

SUPRARENAL AND PITUITARY DEFICIENCY, OBESITY AND MISCELLANEOUS CONDITIONS

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Low metabolic rates are found in conditions in which the thyroid gland does not appear to be involved. It was shown in preceding papers [1] that hypercholesteremia was characteristic of thyroid deficiency regardless of observed metabolic rates. This report therefore deals with observations on the blood cholesterol in other conditions in which hypometabolism was encountered.

In evaluating the basal metabolism test, it is important to remember two things: (1) that it is probably impossible to obtain true basal metabolic rates in some persons because of nervousness or lack of cooperation, and (2) that repetition of the basal metabolism test and keeping the subject in the hospital overnight will tend to give lower readings than are obtained when these procedures are not carried out. In other words, the metabolism is subject to influences which are often beyond the examiner's control. Thus, while groups may show various trends, individual cases may occasionally show no correlation between clinical phenomena and the basal metabolic rate observed.

Is the rate of metabolism dependent on the activity of one endocrine gland? In general practice the basal metabolism is considered as being so closely linked with the thyroid gland that variation in one is considered to indicate a direct or indirect change in the other. If hypercholesteremia is an invariable accompaniment of thyroid deficiency, hypometabolism without hypercholesteremia is dependent on factors other than thyroid.

Three definite clinical conditions of endocrine origin which may lower the metabolism are: thyroid deficiency, or myxedema and cretinism; suprarenal deficiency, or Addison's disease, and hypophyseal

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1. (*a*) Hurxthal, L. M.: Blood Cholesterol in Thyroid Disease: I. Analysis of Findings in Toxic and in Nontoxic Goiter Before Treatment, Arch. Int. Med. **51**:22 (Jan.) 1933; (*b*) Blood Cholesterol in Thyroid Disease: II. Effect of Treatment, ibid. **52**:86 (July) 1933; (*c*) Blood Cholesterol in Thyroid Disease: III. Myxedema and Hypercholesteremia, ibid. **53**:762 (May) 1934.

deficiency associated with pituitary chromophobe tumors.[2] In connection with two of these glands, elevated metabolisms are found when the opposite clinical picture is present, i. e., hyperthyroidism and acromegaly, and in the case of the suprarenal glands, overactivity of the medulla at least will raise the metabolic rate.

There are certain clinical phenomena occurring in connection with the interrelationship of these glands which are well known and which will be mentioned here only as they relate to the blood cholesterol and hypometabolism.

In regard to the relationship between the suprarenal and the thyroid glands, Crile [3] stated the belief that it would be impossible for exophthalmic goiter to develop in a patient with Addison's disease. The question is, therefore, Which is more important in the production of the high basal rates in this disease, the thyroid or the suprarenal glands? Epinephrine excites the patient with hyperthyroidism, but has little effect on the myxedematous patient.[3] Long-standing exophthalmic goiter may produce asthenia and pigmentation, and the basal metabolic rate may not be significantly elevated. This suggests that the thyroid activates the suprarenal glands, which in turn produce the marked nervous symptoms of that disease, and when this nervous energy has been exhausted, the aforementioned type of apathetic hyperthyroidism results. In Addison's disease, on the other hand, if the low metabolic rate were due to an indirect atrophy of the thyroid and thus to thyroid deficiency, administration of thyroid would be helpful; as a matter of fact, it is the consensus that treatment with thyroid is dangerous. If hypometabolism in myxedema likewise were due to an indirect deficiency of the suprarenal glands, cortical extract or epinephrine might be helpful, but it is doubtful if these preparations would effect a cure. That the thyroid is not deficient in Addison's disease is further suggested by the absence of hypercholesteremia. In one case of Addison's disease in which I gave thyroid experimentally, a certain amount of stimulation, the drop in the cholesterol and in the weight and the rise in the pulse rate without apparent influence on the metabolism were suggestive evidence that the thyroid had an effect. It is also probably true that these changes would have come about during the natural progression of the disease. Administration of extract of suprarenal cortex intravenously raised the basal metabolic rate in three days (table 1).

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2. Dr. E. P. McCullagh has called my attention to the finding of hypercholesteremia in hypogonadism (McCullagh, E. P.; McCullagh, D. R., and Hicken, N. F.: Diagnosis and Treatment of Hypogonadism in the Male, Endocrinology **17**:49 [Feb.] 1933).

3. Crile, G. W., and others: Diseases of the Thyroid Gland, Philadelphia, W. B. Saunders Company, 1932, p. 419.

Injections of thyrotropic anterior pituitary extracts have been shown to cause hypertrophy of the thyroid and suprarenal glands, whereas removal of the hypophysis has been followed by atrophy of these organs.[4] So far as I can determine, studies of the blood cholesterol have not been made in these experiments. In five cases of proved [5] pituitary (chromophobe) adenomas with low metabolic rates, the blood cholesterol was not over 200 mg. per hundred cubic centimeters in four male patients, but it was above this value (229 mg.) in the one female

TABLE 1.—*Patients with Addison's Disease*

Serial Number	Age	Sex	Basal Metabolic Rate, per Cent	Pulse Rate	Weight, Lbs.	Deviation in Weight, per Cent	Cholesterol, Mg. per 100 Cc.	
30519	55	M	—29	68	181	+1	153	First observations
			—26	88	165	....	135	After two weeks on desiccated thyroid, 2 grains a day, patient warmer, more active, less sleepy after extract of suprarenal cortex given intravenously
			— 2	80	165	....	...	
30625	58	F	—27	88	106	—21	185	First observation
			—14	88	107	....	189	Six days after extract of suprarenal cortex; death later; autopsy

TABLE 2.—*Patients with Pituitary Chromophobe Adenomas*

Serial Number	Age	Sex	Basal Metabolic Rate, per Cent	Pulse Rate	Weight, Lbs.	Deviation in Weight, per Cent	Cholesterol, Mg. per 100 Cc.	
30671	29	M	—30	62	93	—30	133	Before operation
31869	37	F	—21	70	119	— 8	243	Before operation
			—29	64	114	....	229	After operation
31604	26	M	—18	64	232	+30	116	Before operation
			—34	76	223	....	110	Three weeks after operation
			—27	66	225	....	152	Five weeks after operation
30876	55	M	—33	58	172	+ 9	205	Before operation
32274	45	M	—37	70	124	—20	191	Before operation

(table 2). In none of these patients were there clinical indications of myxedema, a finding which suggests, I think, that the low metabolic rate is not due to a secondary thyroid atrophy. The absence of hypercholesteremia further substantiates this. Collip demonstrated a hormone from the anterior pituitary body which raised the metabolism, yet a rise in the metabolism may take place regardless of hyperplasia in the thyroid. Hyperplasia may indicate merely the effect of the

4. Anderson, E. M., and Collip, J. B.: Thyrotropic Hormone of Anterior Pituitary, Proc. Soc. Exper. Biol. & Med. **3**:680 (Feb.) 1933.

5. These patients were operated on in the neurosurgical section of the clinic by Dr. Gilbert Horrax.

pituitary hormone and not the cause of the elevated metabolism. Hyperplasia of the thyroid in such instances may indicate an attempt to supply the increased demands on the thyroid as the result of increased metabolism instigated by the injection of the anterior pituitary hormone. Clinically, this might be exemplified by active acromegaly, or by the enlargement of the thyroid during the menstrual cycle, at which time, too, the pituitary gland is probably more active than usual. Likewise, the atrophy of the thyroid following hypophysectomy may point to diminished demands on the thyroid as the result of a scaling down of the metabolism, there being no deficiency of thyroxine in relation to bodily needs. Simonds and Helpler,[6] found atrophy of the thyroid as

TABLE 3.—*Patients with Obesity*

Serial Number	Sex	Age	Basal Metabolic Rate, per Cent	Pulse Rate	Weight, Lbs.	Cholesterol, Mg. per 100 Cc.	Deviation in Weight, per Cent
26747	F	32	....	..	...	206	....
26643	F	46	+24	84	200	206	+35
19493	F	43	— 4	78	188	141	+15
20534	F	14	—19	78	148	156	+28
26926	F	10	—24	..	96	179	....
19492	F	16	—23	70	200	137	+56
21312	F	20	—15	67	195	126	+39
20539	F	30	—14	74	175	183	+37
D	F	33	—14	80	161	198	+28
27166	F	46	—10	56	196	234	+28
21102	F	47	—11	78	174	183	+15
24995	F	54	—16	74	163	133	+16
24698	F	55	—15	75	187	183	+35
21149	F	60	—11	76	177	170	+25
26726	F	42	— 7	76	184	248	+42
26242	M	13	—15	80	...	174	....
24951	F	39	— 1	80	161	136	+20
21224	F	45	— 1	66	149	111	+ 8
McC	F	19	— 4	76	230	185	....
17573	F	45	— 1	72	194	176	+43
20997	F	44	....	..	...	188	....
26241	F	35	— 7	86	194	219	+49
30724	F	26	—18	66	152	158	....
26747	F	30	....	..	169	204	....
29578	F	28	....	..	...	180	....

a result of feeding thyroid to dogs. It might be said in this case that, in view of a plentiful external supply of thyroxine, the thyroid atrophies because there is no demand for its secretion. However, when the external supply is cut off, the output of thyroid is insufficient to meet the normal metabolic needs, and hypercholesteremia results. An analogy might be found in the development of a deficiency of insulin after dieting when on the resumption of a normal intake of carbohydrates a decreased tolerance is found.

OBESITY

Determinations of the blood cholesterol were made in twenty-one cases of obesity (table 3). Basal metabolic rates were obtained in

6. Simonds, J. P., and Helpler, O. E.: Fat Tolerance in Experimental Hyperthyroidism, J. A. M. A. **98**:283 (Jan. 23) 1932.

fifteen cases. No attempt was made to place an endocrine label on these cases. Of these patients all except one showed a low metabolic rate, yet the cholesterol values with one exception were within the normal range. The average cholesterol value for the group was 171 mg., and the average metabolism was —13 per cent. These findings are additional evidence that most cases of obesity with low metabolic rates are not of thyroid origin.

That most obesity results from thyroid deficiency is now universally considered as unlikely, yet the conception that a patient with myxedema is always obese still holds fast in the minds of many persons. In forty-five cases of nonoperative myxedema which were observed, 22 per cent of the patients were underweight, 11 per cent of normal weight and 66 per cent overweight. This undoubtedly explains why in so many cases of obesity the question of thyroid deficiency is raised. Some patients with obesity do well when thyroid extract is administered, and others do not. Deficiency in the output of thyroid may increase the weight in one who is naturally obese, but it does not cause obesity in a patient who is usually underweight.

Obesity may not infrequently be associated with thyroid failure and, as pointed out before,[1c] evidence of myxedema may be conceded. There thus would appear to be some logic in carefully considering thyroid deficiency in obesity, and this can be more thoroughly accomplished not only by questioning the patient carefully to elicit some of the more characteristic symptoms of thyroid failure and by obtaining the basal metabolic rate, but also by determining the blood cholesterol. This has been demonstrated to my satisfaction time and again, not only in a few cases following operation on the thyroid, but also in cases of obesity and normal or low metabolic rates.

MISCELLANEOUS CONDITIONS

From the data collected, fifty-six patients with normal thyroid glands on palpation, whose basal metabolic rates were below —9 per cent, were selected. These cases cover a variety of clinical conditions (table 4). For purposes of investigation, desiccated thyroid was prescribed in about one half of the cases, without benefit in most instances. The dose was usually from 1 to 2 grains (0.065 to 0.13 Gm.) of desiccated thyroid a day. This striking failure of thyroid substance to benefit the patient might be attributed to biased judgment. The opinion as to whether or not a given medication is beneficial is often formed from preconceived notions as to its efficacy and not from a critical analysis of the results actually obtained. The mere statement of the patients that they felt better as a result of a prescribed treatment is not always trustworthy evidence of physical benefit. Even though a physical change can be dem-

TABLE 4.—*Patients with Hypometabolism*

Serial No.	Age	Sex	Basal Metabolic Rate, per Cent	Pulse Rate	Weight, Lbs.	Deviation in Weight, per Cent	Cholesterol, Mg. per 100 Cc.	Took Thyroid Extract†	Diagnosis and Comment
26926	10	F	—24	96	145	+100	179	..	Obesity
26292	13	M	—15	80	...	.....	174	+	Obesity
22819	13	F	—22	58	97	— 18	128	+	Malnutrition (later gained 30 pounds; basal metabolic rate still —20)
21442	14	F	—17	84	147	+ 27	133	..	Chorea
20534	14	F	—19	78	148	+ 28	156	+	Obesity
15632	15	F	—15	64	135	+ 10	135	..	Fatigue neurosis
19492	16	F	—23	70	200	+ 56	137	+	Obesity
24880	17	F	—12	78	128	0	160	+	No disease
21952	18	F	—28	66	81	— 35	177	+	Schizophrenia (malnutrition)
24547	19	F	—19	60	144	+ 3	167	+	Fatigue
21312	20	F	—15	67	195	+ 39	126	+	Obesity
21252	20	F	—16	..	121	.....	136	..	Amenorrhea
23672	21	M	—15	51	97	— 31	151	..	Malnutrition; depression
22142	23	F	—19	76	106	— 13	200	..	Manic-depressive psychosis
24347	27	F	—22	52	140	+ 6	185	+	Trophedema
23443	28	F	—10	76	106	— 13	184	..	Chronic salpingitis
20887	29	F	—11	86	138	+ 10	214	+	No disease
20539	30	F	—14	74	175	+ 37	183	+	Obesity
22549	31	F	—11	62	148	+ 10	151	..	Muscle-bound feet
21905	31	F	—21	64	143	— 3	192	..	Cushing's syndrome (proved)
25035	32	M	—17	62	168	+ 6	198	..	No disease
23666	32	F	—22	68	172	+ 33	219	+	Polyglandular syndrome; obesity
23056	32	F	—17	64	120	— 11	156	+	Anemia; fibroid uterus
D.	33	F	—14	80	161	+ 28	198	+	Obesity
24024	33	F	—17	72	145	+ 15	219	+	Chronic arthritis, spine
22636	37	F	—17	68	86	— 30	130	..	Psychoneurosis
23470	38	F	—18	86	109	— 20	171	+	No disease
21338	38	F	—22	68	159	+ 16	176	+	Anxiety neurosis; sleepy and tired
24886	40	F	—11	74	122	— 4	198	..	Cholecystitis, chronic
3366	40	F	—25	68	129	— 2	154	+	Constipation; nervous; "can't take it"
M	14	F	—30	70	116	— 17	154	..	Psychoneurosis
23548	44	F	—15	86	145	— 4	250	..	Psychoneurosis; syphilis; allergy
2212	44	F	—20	75	133	± 0	180	..	Eczema
26833	45	F	—22	80	126	— 12	197	..	Constipation
27166	46	F	—10	56	196	+ 28	234	+	Obesity
19184	46	F	—13	66	140	+ 5	153	+	Sleepy; fatigued
21851	47	F	—24	64	146	— 9	181	..	Hypertension
20093	47	F	—26	56	177	+ 1	195	..	Chronic hypertrophic arthritis
27555	47	F	—13	74	196	+ 41	229	+	Neurosis; obesity
25842	47	F	—14	78	146	+ 7	205	..	Chronic arthritis
21102	47	F	—11	78	174	+ 15	183	..	Obesity
27470	48	F	—22	72	178	+ 26	229	..	Menopause; obesity
27702	49	F	—20	72	140	+ 4	171	+	Hypochromic anemia; felt better on thyroid
28046	49	F	—21	62	137	+ 4	147	..	Hypotension; fatigue
20790	50	F	—18	60	150	— 4	167	+	Migraine; felt better on thyroid, ½ grain daily
21622	51	F	—13	70	151	+ 2	202	..	Aching legs
23390	51	F	—11	72	143	— 2	167	?	Ascariasis; took thyroid 5 years before for headache, with improvement
24995	54	F	—16	74	163	+ 16	133	..	Obesity; chronic arthritis
23981	54	F	—10	85	130	— 6	185	?	Arteriosclerosis
24863	55	F	—18	68	117	— 13	208	..	Multiple sclerosis
17295	55	F	—14	80	173	+ 22	184	..	Paget's disease
24698	55	F	—15	75	187	+ 35	183	+	Obesity; hypertension
29224	56	F	—11	72	107	— 19	205	..	Chronic atrophic arthritis
21149	60	F	—11	76	177	+ 25	170	..	Obesity; arthritis
28011	67	F	—18	48	183	+ 30	167	+	Senile psychosis

† Thyroid appeared to be helpful in only two cases, 20790 and 27702.

onstrated, it does not follow that there existed a specific lack of the particular substance administered. There is little doubt that many patients obtain a real benefit from the use of thyroid extract whether they have a low metabolic rate or not, so that in a sense they may be said to respond to treatment. It is a characteristic feature of most patients with exophthalmic goiter, when the disease is not too severe, to feel well, eat well and sleep well; that this is due to increased secretion of thyroid and the resultant increased metabolic processes cannot, I believe, be denied. I have seen a few patients cured of moderate hyperthyroidism and its annoying symptoms of palpitation, dyspnea, sweating, easy fatigue and the like, who have missed, I am sure, the feeling of well-being at rest which was present before operation. This stimulus undoubtedly can be used to advantage in certain persons, regardless of the level of the basal metabolic rate. It is probable that low basal metabolic rates are found as frequently in normal persons as in the patients seen in the office. But when a low basal metabolic rate is discovered in a more or less exhaustive survey for diagnosis, it may be regarded as evidence of hypothyroidism; thyroid is then prescribed in some form, the patient feels better, and the conclusion is thyroid deficiency. This is not rational but empirical therapy and leads only to confusion in the field of endocrinology.

Thyroid extract has been used in the treatment of chronic arthritis, and low basal metabolic rates are occasionally found in these cases. Its use may originally have suggested itself as the result of some striking case of myxedema in which symptoms of the joint were predominant. The rationality of its use now lies partly in the increased flow of blood associated with mild, induced hyperthyroidism. I can recall only two cases of myxedema in which symptoms of the joint were given as the chief complaint, although it is frequently a secondary complaint. In fifteen cases of chronic hypertrophic arthritis, the cholesterol values were above the normal range in two patients, one of whom had a basal metabolic rate of —2 per cent; in the other, the basal metabolic rate was not determined. I have not observed definite benefit from the use of desiccated thyroid in arthritic cases.

CONCLUSIONS

1. Hypometabolism associated with known suprarenal or pituitary insufficiency was not accompanied by hypercholesteremia in this series.

2. Obesity was usually accompanied by relative hypometabolism and a normal blood cholesterol. If hypercholesteremia is found, there may be an associated or concealed myxedema.

3. Hypometabolism found in miscellaneous clinical conditions is probably not due to thyroid failure in view of the absence of hypercholesteremia.

MALIGNANT HYPERTENSION: THE HISTOLOGIC CHANGES IN THE KIDNEYS

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The relationship of arterial disease to disease of the kidneys is far from accurately settled.[1] As a contribution to the subject I determined, in twenty-seven cases, the size and the weight of the kidneys and the ratio of the wall to the lumen of the renal arterioles in relation to histologic renal changes. So far as I know, this is the largest series of cases in which both a clinical diagnosis of malignant hypertension and a histologic study of the tissue obtained at necropsy have been made.

Consciously, or without elaborately detailed distinction, most physicians have considered various grades of severity in cases of arterial hypertension. Perhaps Volhard and Fahr,[2] in 1914, were most definite in this regard. For them there was a *bösartige* type distinct from a milder one. Later Fahr [3] used the term malignant nephrosclerosis to indicate the picture presented by the kidneys in a severe type of disease. In 1924, Keith and Wagener [4] separated and identified a group of cases more definitely, establishing a clinical basis for diagnosis. This consisted in a sustained, elevated blood pressure combined with neuroretinitis, but without appreciable anemia or impairment of the renal function until the later stages of the disease. Fuller elaboration of this concept is contained in more recent reports by Keith, Wagener

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This article is the abridgment of a thesis submitted to the faculty of the Graduate School of the University of Minnesota in partial fulfilment of the requirements for the degree of Master of Science in Medicine. The work was done under the direction of Dr. N. M. Keith, Division of Medicine, and Dr. J. W. Kernohan, Section on Pathologic Anatomy, the Mayo Clinic.

1. Moschcowitz, Eli: Hypertension: Its Significance, Relation to Arteriosclerosis and Nephritis and Etiology, Am. J. M. Sc. **158**:668 (Nov.) 1919.

2. Volhard, F., and Fahr, T.: Die Brightsche Nierenkrankheit, Berlin, Julius Springer, 1914.

3. Fahr, T.: Kurze Beiträge zur Frage der Nephrosklerose, Deutsches Arch. f. klin. Med. **134**:366, 1920.

4. Keith, N. M., and Wagener, H. P.: Cases of Marked Hypertension, Adequate Renal Function and Neuroretinitis, Arch. Int. Med. **34**:374 (Sept.) 1924.

and Kernohan.[5] The short duration of symptoms, the tendency to affect comparatively young persons and the maintenance of good renal function until a late stage were predominant features in the majority of cases. It is impossible at present to indicate a single test of renal function which may not be criticized for one reason or another. Hence, it is difficult, even when many methods of examination are used, to determine precisely early stages of renal injury. Major[6] stressed this feature in particular and suggested additional methods.

The reports of cases given at the end of this paper have been abbreviated from histories in the files of the Mayo Clinic. So far as possible all factors relative to previous illnesses, occupational or otherwise, poisoning, familial tendencies, age, sex, duration of symptoms and mode of onset have been considered with the findings on physical examination.

These cases have been considered as belonging to the group of malignant hypertension or diffuse arterial disease with hypertension, group 4. Each case had been carefully considered, and the data given in the abbreviated reports constitute only a bare abstract of the essential clinical features. The duration of symptoms was in no case greater than five years, and the known duration of the elevation of blood pressure was as short as nine months (case 20). Medication consisted, in most cases, only of sedatives such as chloral hydrate or barbiturates. When indicated, as when vomiting was persistent, intravenous medication had been given.

Laboratory data in respect to the range of elevation of the blood pressure, urinary excretion, presence of anemia and serologic examination are contained in table 1. In most instances the determinations were made while the patients were in the hospital and usually indicate findings made shortly before death. In case 26, the Kline and Kahn flocculation tests were used as serologic tests for syphilis. The Wassermann reaction was used in all other cases. Values for the blood urea were determined shortly before death. Often estimations had been made earlier, and similar values had not

5. (*a*) Keith, N. M.: Classification of Hypertension and Clinical Differentiation of the Malignant Type, Am. Heart J. **2**:597 (Aug.) 1927. (*b*) Keith, N. M.; Barker, N. W., and Kernohan, J. W.: Histologic Studies of the Arterioles in Various Types of Hypertension, Tr. A. Am. Physicians **46**:66, 1931. (*c*) Keith, N. M.; Wagener, H. P., and Kernohan, J. W.: The Syndrome of Malignant Hypertension, Arch. Int. Med. **41**:141 (Feb.) 1928. (*d*) Kernohan, J. W.; Anderson, E. W., and Keith, N. M.: The Arterioles in Cases of Hypertension, Arch. Int. Med. **44**:395 (Sept.) 1929. (*e*) Wagener, H. P.: Sclerosis of the Retinal Arterioles, Arch. Ophth. **3**:335 (March) 1930; (*f*) Retinal Vascular Changes in Hypertension, Ann. Int. Med. **4**:222 (Sept.) 1930.

6. Major, R. H.: Renal Function in Arterial Hypertension, Am. J. M. Sc. **176**:637 (Nov.) 1928.

TABLE 1.—*Laboratory Data for the Twenty-Seven Cases Reported*

Case	Blood Pressure, Mm. of Mercury: Maximal: Systolic	Maximal: Diastolic	Minimal: Systolic	Minimal: Diastolic	Specific Gravity of Urine: Lowest	Specific Gravity of Urine: Highest	Albumin in Urine, Grade	Leukocytes in Urine, Grade	Erythrocytes in Urine, Grade	Casts, Grade	Urea, Mg. in 100 Cc. Whole Blood	Creatinine, Mg. in 100 Cc. Whole Blood	Uric Acid, Mg. in 100 Cc. Whole Blood	Sulphates, Mg. in 100 Cc. Serum	Chlorides, Mg. in 100 Cc. Plasma	Urea Clearance*	Phenolsulphonphthalein Excretion, per Cent	Hemoglobin, per Cent (Dare)	Hemoglobin, Gm. in 100 Cc. Blood	Erythrocytes, Millions per C.Mm. of Blood	Leukocytes per C.Mm. of Blood	Flocculation Test for Syphilis (Blood)
1	255	165	200	150	1.006	1.025	1	1	..	1	34	1.9	...	.....	...	....	...	82	....	5.11	13,000	Negative
2a†	240	160	210	160	.....	1.018	1	1	..	1	33	1.8	...	.....	...	....	40	70	....	4.71	10,400	Negative
2b†	...	...	...	...	.....	.....	..	..	..	..	134	7.4	4.6	.....	...	....	..	70	....	4.00	16,500	
3	240	140	222	130	.....	.....	..	..	..	..	63	2.6	3.8	.....	...	....	..	..	....	....	.....	Negative
4a	204	108	170	90	1.001	1.025	1	3	..	1	100	3.4	4.5	.....	...	....	25	..	13.8	3.52	12,600	Negative
4b	238	154	220	144	1.020	.....	2	1	..	1	115	4.1	4.6	.....	555	....	..	..	11.2			
5	240	120	...	...	1.001	.....	..	..	..	..	101	4.5	...	.....	...	....	..	..	....	3.75	16,800	Negative
6	268	150	216	120	1.011	.....	2	1	..	..	148	6.6	...	.....	...	....	..	..	....	3.80	12,400	Negative
7	220	168	168	128	1.015	.....	4	1	..	..	384	16.0	...	.....	530	....	0	65	....	4.07	8,800	Negative
8	230	110	...	...	1.012	.....	1	1	..	..	242	10.4	...	.....	...	....	..	40	....	2.56	8,200	Negative
9	230	165	150	110	1.013	.....	1	1	..	..	224	9.5	...	.....	...	....	10	65	....	3.48	8,700	Negative
10‡	190	156	148	102	1.017	1.020	..	1	..	..	40	....	...	.....	525	....	50	..	....	4.96	11,800	Positive
11	270	164	175	120	1.010	1.020	3	1	..	1	651	35.2	...	148.9	...	....	..	73	....	4.27	8,400	Negative
12	220	132	...	...	1.010	.....	3	1	1	1	132	5.4	...	.....	...	....	10	60	....	3.22	5,600	Negative
13	240	120	180	90	1.015	1.022	2	2	..	1	110	1.8	...	.....	579	....	35	80	....	4.50	8,500	Negative
14	300	140	170	90	1.001	1.018	2	1	1	..	102	1.6	...	.....	...	....	15	70	....	4.24	.....	Negative
15a	158	110	118	80	1.007	.....	1	1	1	1	31	1.5	2.9	.....	564	....	65	75	....	4.45	.....	Negative
15b	250	170	185	135	1.009	.....	1	..	..	..	271	17.0	...	.....	495	....	0					
16	240	144	224	140	1.018	.....	3	1	..	2	252	6.4	...	.....	...	....	..	60	....	3.04	.....	Negative
17	280	190	232	134	1.010	1.012	4	1	..	..	36	1.9	...	.....	...	....	..	55	....	3.46	10,800	Negative
18	236	150	190	120	1.016	.....	3	1	1	2	246	....	...	.....	...	....	..	..	....	....	.....	Negative
19	220	140	210	133	1.012	.....	3	1	2	..	444	20.0	...	.....	495	....	..	40	...	2.48	19,900	Negative
20a	112	80	...	...	1.016	1.030	0	1	..	..	40	2.0	...	.....	...	....	..	95	....	....	18,100	Negative
20b§	180	110	...	...	1.016	.....	2	1	1	2	132	2.4	...	.....	...	....	..	60	....	....	17,000	
21	260	150	220	124	1.013	.....	3	1	1	1	243	9.2	...	.....	...	....	..	58	....	3.03	19,800	Negative
22	230	165	225	160	1.013	.....	2	..	..	..	20	....	...	6.03	...	....	48	104	....	5.20	11,200	Negative
23	250	110	190	110	1.010	.....	1	1	3	..	215	13.2	...	.....	...	....	10					
24	200	130	170	120	1.002	1.030	2	..	..	1	40	1.5	...	.....	...	23.3	50	..	16.7	4.20	7,000	Negative
	200	150	...	...	.....	.....	3	1	1	1	156	3.0	...	10.5	...	....	..	..	12.3	3.76	13,000	
25	192	126	172	110	1.005	.....	4	1	2	..	232	13.6	...	35.8	...	....	..	80	....	4.69	18,400	Negative
26‖	190	130	116	92	1.010	.....	2	1	1	..	303	20.3	...	26.3	520	2.1	..	..	11.8	3.33	9,800	Positive
27	280	175	200	95	1.013	.....	3	1	..	..	256	....	...	.....	...	....	..	..	9.6	3.14	20,100	Negative

* This indicates cubic centimeters of blood cleared of urea by the kidneys each minute.
† In each case in which a and b appear they indicate, respectively, first and second admission.
‡ The flocculation test for syphilis, on cerebrospinal fluid, was positive.
§ The urine contained arsenic and lead.
‖ The urine contained arsenic.

been obtained. The figures for specific gravity of urine were obtained on numerous routine examinations or were obtained by estimation of the ability of the kidney to dilute or concentrate urine. In any case, these figures were obtained, unless otherwise stated, from examinations made shortly before death. The maximal and minimal blood pressures were either the extremes of blood pressure found on hourly examination for twenty-four hours or were simply the highest and lowest figures derived from a number of examinations.

Consideration of the abbreviated reports of cases and of the laboratory data given in table 1 suggests some features common to all of the cases. The ages of the patients ranged from 22 to 72; in sixteen of the twenty-seven cases death occurred when the patient was in the fourth or fifth decade of life. Three patients were younger than this at death; the others were older. Disability was of relatively short duration. The symptoms varied widely. In all of the cases, characteristic ocular findings as outlined by Wagener [5f] were demonstrated. Except in cases 10, 17 and 22, there was evidence of impairment of excretion of nitrogenous products before death. In cases 10 and 22 there was no opportunity to obtain blood for examination in the late stages of the disease. Death in case 17 was probably the result of cerebral complications. The rapidity of onset of impairment of excretion of nitrogen in cases 19, 20 and 24 was striking; the patients had been under observation for considerable periods, and renal function was closely watched. In all cases, readings of blood pressure were invariably high, and there was little fluctuation in the level of either systolic or diastolic pressure.

Definite evidence of syphilitic infection was available in cases 10 and 26, and the history of miscarriages was suggestive in case 17. A history of either scarlatina or repeated attacks of tonsillitis was forthcoming in seventeen cases. One patient (case 15) had been treated five years previously for acute nephritis with edema. The presence of lead and arsenic in the urine in case 20 and of arsenic in case 26, and the administration of compounds of mercury in cases 24 and 15 were the only suggestions that metallic poisoning was a factor in the disease. Excessive use of tea, coffee, alcohol or tobacco was a significant feature only in cases 4, 8 and 20.

In all of the cases both kidneys or portions of them had been preserved in formaldehyde. From these, sections for microscopic examination were taken and stained with hematoxylin and eosin, Weigert's elastic tissue stain, van Gieson's stain, Mallory-Heidenhain's azan-carmine stain (as modified by Galantha) and sudan III with methylthionine chloride, U. S. P. (methylene blue). There was a noticeable increase in the thickness of the walls of the smaller arteries. To establish this with more certainty and to compare the increased thickness of the wall

with the diameter of the arterial lumen, various measurements were made with a Bausch and Lomb micrometer according to a method commonly used and described in detail by Kernohan.[5d] In short, it consists in measuring the wall of the artery at four points, each situated at either end of lines drawn at right angles to each other through the center of the lumen. The average of these four measurements is then compared with the average diameter of the lumen. From these the ratio of the wall to the lumen is established. In each case at least ten arterioles, the outside diameters of which varied from 60 to 180 microns, were meas-

TABLE 2.—*Combined Weight of the Kidneys and the Ratio of the Walls to the Lumens of the Renal Arterioles*

	Malignant Hypertension		Controls	
Case	Weight, Gm.	Ratio of Wall to Lumen	Specimen	Ratio of Wall to Lumen
1	270	1:0.7	1	1:1.9
2	302	1:0.6	2	1:2
3	247	1:0.8	3	1:1.7
4	194	1:0.3	4	1:1.26
5	206	1:0.5	5	1:1.7
6	237	1:0.5	6	1:1.24
7	340	1:0.8	7	1:1.9
8	285	1:0.5	8	1:2.2
9	120	1:0.9	9	1:2.5
10	233	1:0.7		
11	243	1:0.4		
12	225	1:0.6		
13	221	1:0.5		
14	265	1:0.6		
15	Not available	1:0.6		
16	218	1:0.5		
17	268	1:0.7		
18	205	1:0.5		
19	380	1:0.3		
20	213	1:1.3		
21	388	1:0.5		
22	200	1:0.9		
23	309	1:0.6		
24	254	1:0.8		
25	341	1:0.6		
26	216	1:0.7		
27	289	1:0.7		

ured. Only those in which the planes of section passed at right angles through the vessel were measured. As controls, sections from the kidneys of nine young adults who had died as a result of accident or of cerebellar tumors were considered. In none of these was there evidence clinically or on postmortem examination of renal disease. Measurements of arterioles were made. These are included in table 2, with the similar ratio of wall to lumen found in the kidneys in the twenty-seven cases under consideration.

In twenty-six cases the weights of the kidneys were available; they are recorded in table 2. They varied considerably, but on the whole were surprisingly large. The average combined weight was 261 Gm. Although the body weights were available, their accuracy could be questioned, since some patients had been edematous when examined, whereas

others had vomited for varying periods before seeking medical attention. Concerning case 9 only the term contracted kidney might be used. In all other cases the kidneys could safely be considered to be of normal size.

There were some interesting findings on gross examination at necropsy. In all cases the heart had undergone hypertrophy. Evidence of healed tuberculosis of the lungs or lymph nodes was forthcoming in nineteen cases. Definite pyelonephritis was evident in cases 5, 25 and 27.

On microscopic examination more or less advanced disease was found in every case. It involved almost all of the structures of the kidney to a variable degree: glomeruli, tubules, arteries and interstitial tissue. The veins and venules did not seem involved, except for dilatation in some instances.

Changes in the glomeruli varied rather widely. In most cases either complete or partial hyalinization was present. In each case, one hundred or more glomeruli were examined, and the percentage of glomeruli presenting complete hyalinization varied, ranging from 2 to 35. Only in case 20 (symptoms of only nine months' duration) were no completely hyalinized glomeruli seen. In all of the cases many of the glomeruli showed partial hyaline change. The use of the term hyaline requires some explanation. Wells [7] stated: "There is no one chemical compound hyaline which accumulating in cells or tissues produces a hyaline appearance. The limitations of the application of the term hyaline degeneration are not agreed on but, in general, it is used to apply to clear homogeneous pathological substances that possess a definite affinity for acid stains such as eosin." The preparations treated with van Gieson stain showed that even when the glomerulus had been completely replaced by this material, a connective tissue fiber could not be demonstrated throughout. In most cases a thick, reddish border could be seen, and, in a few, the reddish fibers extended into the center of the structureless nodules, from what was probably the point of entrance of the afferent artery. McGregor [8] showed that connective tissue cells normally extend into the glomerulus in this region. Partial hyalinization of a glomerulus was frequently seen. Either one loop or the portion of the glomerulus that was continuous with the afferent artery had undergone this change.

Points of adhesion of glomerular loops to Bowman's capsule were frequently seen. In the preparation stained with azan-carmine it was noticed that at these points the blue-stained basement membrane of the

7. Wells, H. G.: Chemical Pathology, ed. 4, Philadelphia, W. B. Saunders Company, 1920.

8. McGregor, Leone: The Finer Histology of Normal Glomerulus, Am. J. Path. **5**:545 (Nov.) 1929; Histological Changes in the Renal Glomerulus in Essential (Primary) Hypertension, ibid. **6**:347 (May) 1930.

capsule appeared continuous with the basement membrane of the glomerular loop, which in many instances appeared thickened. The van Gieson preparations failed to bring out a reddish fiber in these areas. With these adhesions, another feature could be noted: The glomerular loops were less numerous than in other glomeruli and appeared flatter. In most cases, however, glomerular capillary spaces were open and contained erythrocytes. Very few polymorphonuclear leukocytes were seen in these loops, and in no instance were erythrocytes or leukocytes seen in the capsular space. Neither was a definite formation of crescents seen, although in a few instances the point of

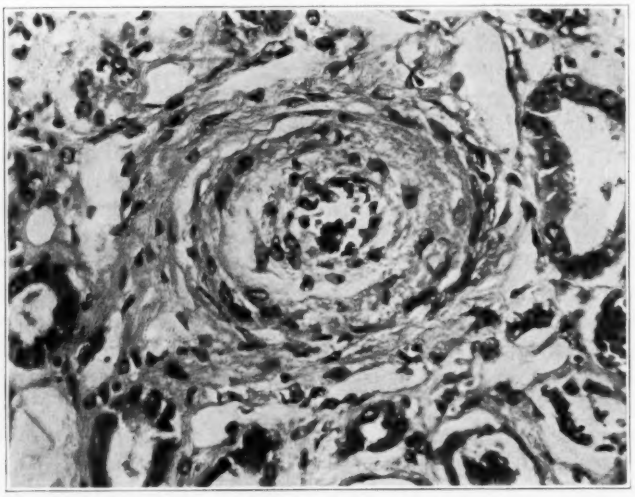

Fig. 1 (case 11).—Changes in an artery of medium size; thickening of both medial and intimal tunics. Hematoxylin and eosin; × 300.

adhesion of a glomerular loop to the capsule suggested this formation. Often there appeared to be many more nuclei of cells within the glomerulus than normally. This suggested that the entire glomerulus was larger than others. The apparent proliferation of endothelial and epithelial cells was not, however, a constant feature. Only rarely were lipoid droplets identified in the glomeruli, even in those which exhibited the most extensive hyaline change.

The smaller arteries presented the most striking feature in all of the sections. Invariably the lumens were smaller than normal and, relative to the thickness of the wall, were very much diminished in size. Not a few were completely closed. The cause of this real or apparent thickening of the wall appeared to arise from a number of factors (fig. 1).

Beneath the endothelium there was usually a zone, in which few, and in many cases no, nuclei could be seen. This zone stained a uniform reddish pink in the hematoxylin-eosin, a light blue in the azan-carmine and a faint yellow in the van Gieson preparations. In this area of sections stained with sudan III, invariably there were a few fine, reddish points. Often a red band partly or completely encircled the vessel (fig. 2). The latter feature was rarely noticed in larger arteries. The internal elastic lamina could be seen clearly in the Weigert preparations. It was always thickened; in many instances it was broken and irregular (fig. 3) and in a few cases appeared to be separated into a number of

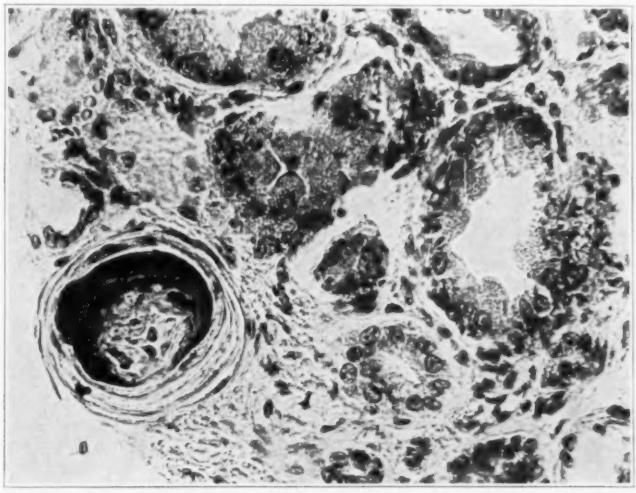

Fig. 2 (case 25).—Fatty change in the arterial wall. This appears as a dark smudge almost encircling the lumen. Sudan III; × 300.

strands. The tunica media rarely presented degenerated areas. Only occasionally were reddish granules visible in the sudan III preparations. In most cases there was an apparent increase in the number of nuclei in the media. Only in the case of arteries of medium and large size was a definite, thickened fibrous band surrounding the adventitial tunica seen in the van Gieson preparations. Changes in the endothelium itself were somewhat difficult to determine. There was always the appearance of crowding of the nuclei of cells (fig. 4). It is evident that this might be due to proliferation of the endothelium, or it might be debated that originally these endothelial cells surrounded a larger lumen and were now forced into a smaller space by reason of the thickened walls.

Fig. 3 (case 13).—Thickening and fragmentation of the elastic lamina. Weigert's elastic tissue stain; × 300.

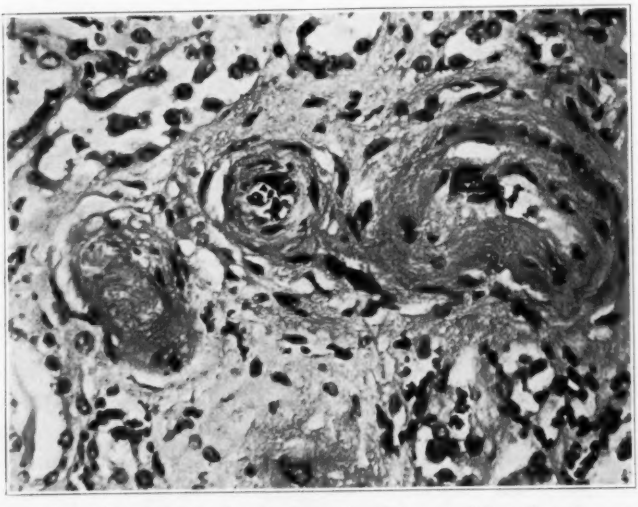

Fig. 4 (case 18).—Thickening in the walls of the arterioles; there is an apparent increase in the number of the nuclei in the endothelium. Hematoxylin and eosin; × 300.

The ratios of the wall to the lumen are given in table 2. These are somewhat smaller than those obtained by Kernohan and by Pilcher and Schwab.[9] Comparisons cannot be too literal. The material used by Kernohan [5d] was obtained from muscle which had been taken for biopsy. Specimens here considered had been preserved for varying periods, and tissue fixatives may have had some effect. Furthermore, if the disease is rapidly progressive, it would be reasonable to postulate that the change in material obtained at necropsy would be more advanced than in that obtained for biopsy. It is probably safe to assert that the ratio of wall to lumen in these renal arterioles is reduced to less than

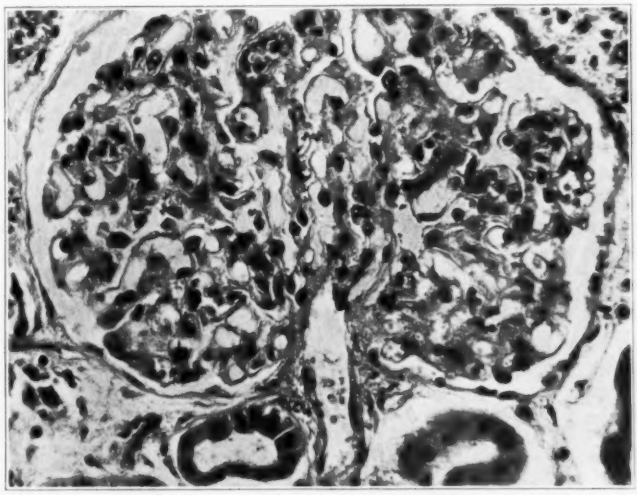

Fig. 5 (case 9).—Dilated vas afferens. Hematoxylin and eosin: × 300.

1:1, and to appreciably less than that reported from examination of arterioles in voluntary muscle.

It has been mentioned that there was a dilated vessel continuous with the glomerular capillaries. In many cases this was the efferent vessel, but in a few instances examination of two or three successive sections established its identity as the afferent vessel (fig. 5). In such cases its wall presented a hyaline change similar to that seen in other small arteries in the section. Rarely was a small group of erythrocytes seen external to the endothelium, in the substance of the tunica media.

Tubular change, although less striking, was definite. In no case was swelling of the epithelial cells sufficient to occlude the lumen of the

9. Pilcher, J. F., and Schwab, E. H.: Arteriolar Changes in Essential Hypertension, Texas State J. Med. **28**:665 (Feb.) 1933.

tubule. This had been suspected in cases in which concentrated solutions of dextrose had been given intravenously; Helmholz [10] found this experimentally in some animals to which concentrated solutions of sucrose had been given. In many areas the epithelium was flattened and the entire tubule dilated. Groups of dilated tubules of this sort were often seen and gave the appearance of small cysts. Masses were frequently seen within tubules. Usually they were homogeneous and structureless; they have been considered to be casts. Leukocytes, desquamated epithelial cells and erythrocytes often were found alone or surrounding the casts. Frequently, small granules could be identified in the cytoplasm of the epithelial cells, but rarely were lipoid droplets seen in the sudan III preparations. Sometimes in the azan-carmine preparations the basement membrane of the tubule appeared thickened.

Changes in the interstitial tissue could be found consistently. These varied in extent, but there was always more or less connective tissue between the tubules, especially in the medulla, with scattered groups of cells with small nuclei. These groups of small cells were mainly lymphocytes, with an occasional polymorphonuclear leukocyte and some plasma cells. They bore no clear relationship to glomeruli or tubules. In many cases the veins and capillaries around and between tubules were distended with erythrocytes.

In no case in which metallic poisoning or syphilis could have been considered as an etiologic factor was there a peculiar pathologic process. Tonsillitis or other infections had been noted in a high proportion of the cases. It is dangerous to interpret findings as being due to these infections. Evidences of tuberculosis were forthcoming in as high a proportion of cases, and it has not been suggested that this disease is an etiologic factor in the production of hypertension.

That changes in the blood or vascular structures of the body are factors in renal disease was suggested by Bright.[11] Gull and Sutton,[12] in reference to the constitutional form of Bright's disease, stated that the morbid condition begins as fibrosis in and around the small arteries and capillaries in the intertubular tissue. They also described a great change and degeneration of the arteries and the deposition of new material external to the lumen of the vessel. Johnson [13] disagreed in part and considered that there is actual hypertrophy of the arterioles.

10. Helmholz, H. F.: Personal communication to the author.

11. Bright: Cases and Observations Illustrative of Renal Disease Accompanied with the Secretion of Albuminous Urine, Guy's Hosp. Rep. **1**:338, 1836.

12. Gull, William, and Sutton, quoted by Gull, William: Arterio-Capillary Fibrosis, Brit. M. J. **2**:673 (Dec. 21) 1872.

13. Johnson, George: The Muscular Arterioles: Their Structure and Function in Health and Certain Morbid States, Brit. M. J. **1**:443 (April 14) 1877.

Ziegler [14] stated that widespread sclerosis—sometimes necrosis in the intima of small arteries—produces contracted kidney. He mentioned changes in the tubules as a result. Ewald,[15] in considering the changes in the smaller vessels in renal disease, measured the vessels, finding in normal vessels a ratio of wall to lumen of 0.1 : 1 or 0.2 : 1 and in renal disease a greatly changed ratio, sometimes 1.2 : 1. Thoma,[16] in an investigation into the injury to the circulation of the blood in chronic interstitial nephritis, studied the new formation of connective tissue in the umbilical artery, the ductus Botalli and the arteries in the stumps of amputated limbs. He mentioned the appearance of a hyaline substance rich in cells under the intima. He found by perfusion that there was a decreased flow of fluid through the renal vascular bed. Mahomed [17] mentioned a prealbuminuric stage of Bright's disease and considered poisoned blood as a factor in producing impeded circulation, which leads to high blood pressure. Allbutt [18] found that in many of these cases of prealbuminuria Bright's disease developed.

Further consideration of the arterioles of the kidneys and of the systemic circulation has been reported by Kernohan, Anderson and Keith and by Murphy and his associates,[19] who included measurements of the walls and lumens of smaller arteries and arterioles. They concluded that the ratio of the wall to the lumen was much decreased. Ghoreyeb [20] and Baehr, in investigating the condition of the arterial bed by perfusion and injection, found it contracted. The former found the same impediment to perfusion in spontaneous disease of the kidney

14. Ziegler, E.: Ueber die Ursachen der Nierenschrumpfung nebst Bemerkungen über die Unterscheidung verschiedener Formen der Nephritis und die darauf bezüglichen Theorien, Deutsches Arch. f. klin. Med. **25**:586, 1880.

15. Ewald, C. A.: Ueber die Veränderungen kleiner Gefässe bei Morbus Brightii, Virchows Arch. f. path. Anat. **71**:453 (Dec.) 1877.

16. Thoma, R.: Zur Kenntnis der Circulationsstörung in den Nieren bei chronischer interstitieller Nephritis, Virchows Arch. f. path. Anat. **71**:42 (Sept.) 1877; Ueber die Abhängigkeit der Bindegewebsneubildung in der Arterienintima von den mechanischen Bedingungen des Blutumlaufes, ibid. **95**:294 (May) 1880; **104**:209, 1886.

17. Mahomed, F. A.: Some of the Clinical Aspects of Chronic Bright's Disease, Guy's Hosp. Rep. **24**:363, 1879.

18. Allbutt, Clifford: Diseases of the Arteries, Including Angina Pectoris, London, The Macmillan Company, 1915.

19. Murphy, F. D., and Grill, John: So-Called Malignant Hypertension, a Clinical and Morphologic Study, Arch. Int. Med. **46**:75 (July) 1930. Murphy, F. D.; Grill, John; Pessin, Benjamin, and Moxon, G. F.: Essential (Primary) Hypertension, Ann. Int. Med. **6**:31 (July) 1932.

20. Ghoreyeb, A. A.: Studies on the Circulation: I. The Effect of Disease on the Renal Arterial Bed, J. M. Research **35**:87 (Sept.) 1916; A Study of the Mechanical Obstruction to the Circulation of the Kidney Produced by Experimental Acute Toxic Nepropathy, J. Exper. Med. **18**:29 (July) 1913.

produced by potassium chromate. In 1904, Jores [21] emphasized the degenerative nature of the arterial changes in contracted kidney. From Fahr,[22] however, came the greatest emphasis on the distinction between benign and malignant nephrosclerosis. The latter occurred in younger persons. Microscopically, there was an endarteritic and necrotizing process in the arterioles. These vessels were often narrowed and many times completely closed. Arteriosclerosis of the larger arteries was also present.

It is to be remembered, as Johnson suggested, that occlusion of the lumens of arteries may not be so great as it seems to be in some sections. Shapiro [23] found, by perfusion, that india ink passed through arteries which were apparently occluded. He further stated that although ischemia undoubtedly is present in nephrosclerosis, it is not the basis of the characteristic pathologic change. He considered direct hyperemia to be the cause and distinguished the appearance of well filled veins and capillaries from the condition seen in chronic passive congestion of the kidney. Ettinger [24] produced contraction of arterioles, fibrosis and hyalinization of some glomeruli, with occasional areas of fatty degeneration and adhesions of glomerular loops to Bowman's capsule. Bell and Clawson [25] stated that in the glomeruli of four of a group of thirty-six cases which constituted their renal group showing hypertension, there were acute inflammatory changes such as are found in glomerulonephritis. They commented on the evidence of most rapid closure of small arteries and arterioles.

In an examination of fifteen cases of essential hypertension, Pilcher and Schwab found a difference between the arteriolar change seen in the kidney and spleen and that seen in the liver and pancreas. In the former two organs, degenerative changes were prominent. In an interesting report of a case in which a kidney was removed because of hematuria and in which death occurred shortly afterward, but in which clinical studies following the emergency nephrectomy established the

21. Jores, L.: Ueber Arterienveränderungen bei Nephritikern, Verhandl. d. deutsch. path. Gesellsch. **7**:174, 1904; Ueber den pathologischen Umbau von Organen (Metallaxie) und seine Bedeutung für die Auffasung chronischer Krankheiten insbesondere der chronischen Nierenleiden (Nephrozirrhosen) und der Arteriosklerose, Virchows Arch. f. path. Anat. **221**:14, 1916.

22. Fahr, T.: Zur Pathogenese der akuten Glomerulonephritis, Deutsche med. Wchnschr. **52**:735 (April) 1926.

23. Shapiro, P. F.: Malignant Nephrosclerosis, Arch. Int. Med. **48**:199 (Aug.) 1931.

24. Ettinger, G. H.: The Action of Janus Green upon Blood Vessels, Quart. J. Exper. Physiol. **22**:167 (Aug.) 1932.

25. Bell, E. T., and Clawson, B. J.: Primary (Essential) Hypertension, Arch. Path. **5**:939 (June) 1928.

diagnosis of malignant arterial hypertension, Weiss, Parker and Robb [26] stated that there was proliferation of the glomeruli of definite degree and a more marked degree of cellular infiltration in the kidney that was removed first.

The medical literature of the last two decades contains many articles on the various features presented by kidneys removed in cases of hypertension. Since the etiology of the primary condition remains obscure, the causal factors are also conjectural. Volhard [27] mentioned the possibility that an inflammatory factor aggravated or was added to preexisting vascular disease. In considering the pathogenesis of acute glomerulonephritis, Fahr showed that early in this condition (three days after its onset) there were evident changes in the afferent and efferent glomerular arteries. Gaskell [28] had shown much earlier that in many cases of acute glomerular nephritis fatty and hyaline changes could be found in the intima of the afferent artery of the glomerulus. Löhlein [29] emphasized changes in this artery and described dilatation of its lumen. Klemperer and Otani [30] agreed with Löhlein that the tempo of the process distinguishes mild arterial disease from malignant nephrosclerosis. They considered a group in which they postulated an inflammatory factor. Herxheimer [31] and Stern [32] reported cases of arteriolonecrosis in which they considered that there had been no arteriolitis, and that the rapid development of renal insufficiency was the result of a purely necrotizing process. Baehr and Ritter [33] considered that there can develop in chronic nephritis vascular alterations as severe as those in primary disease of the intrarenal vessels. Fishberg [34] asserted that many types of arteriosclerosis and hypertrophy of the muscular layer can

26. Weiss, Soma; Parker, Frederic, Jr., and Robb, G. P.: A Correlation of the Hemodynamics, Function and Histologic Structure of the Kidney in Malignant Arterial Hypertension with Malignant Nephrosclerosis, Ann. Int. Med. **6**:1599 (June) 1933.

27. Volhard, F.: Die doppelseitigen hematogenen Nieren-Erkrankungen, Berlin, Julius Springer, 1918, vol. 8.

28. Gaskell, J. F.: On the Changes in Glomeruli and Arteries in Inflammatory and Arterio-Sclerotic Kidney Disease, J. Path. & Bact. **16**:287, 1912.

29. Löhlein, M.: Zur vasculären Nierensklerose, Med. Klin. **2**:1042, 1916.

30. Klemperer, Paul, and Otani, Sadao: Malignant Nephrosclerosis (Fahr), Arch. Path. **11**:60 (Jan.) 1931.

31. Herxheimer, Gotthold: Ueber Arteriolonekrose der Nieren, Virchows Arch. f. path. Anat. **251**:709, 1924.

32. Stern, Max: Ueber einen besonders akut verlaufenen Fall von Arteriolonekrose der Nieren mit dem makroskopischen Bilde der grossen bunten Niere, Virchows Arch. f. path. Anat. **251**:718, 1924.

33. Baehr, George, and Ritter, S. A.: Arterial Supply of the Kidney in Nephritis, Arch. Path. **7**:458 (March) 1929.

34. Fishberg, A. M.: The Arteriolar Lesions of Glomerulonephritis, Arch. Int. Med. **40**:80 (July) 1927.

develop in glomerulonephritis. Russel [35] considered that degenerative vascular changes supervene on hypertrophy.

Changes in the tubules are usually found, and these have also been related to the alteration in circulation, since any impairment of the blood supply of the glomerulus must affect the tubule proceeding from it. Jores disagreed with the usual interpretation and asserted that the atrophy which resulted was atrophy from inactivity. He also considered elastic hyperplasia and fatty degeneration of the arteriolar walls as factors in the production of the disease. In the main, Aschoff [36] agreed with this interpretation.

In three of the cases on which this study is based evidence of pyelonephritis was present. Braasch [37] reported four cases of urinary obstruction from various causes in which at necropsy thickening of the tunica intima of the arteries could be demonstrated. Russel, in an exhaustive investigation of a large group of cases, stated: "The type of nephritis which is closely associated with chronic degeneration of arteries is, therefore, also found in association with compression of the renal cortex by hydronephrosis, tumors or cysts."

REPORT OF CASES

CASE 1.—A white housewife, aged 45, first noted weakness of the right side of the body. Other symptoms were impaired vision, dyspnea, edema and headache. The significant findings on physical examination were an enlarged heart, an enlarged liver, right hemiparesis and edema. Later, paresis increased. Previous illnesses included scarlatina and influenza. Sclerosis of the peripheral arteries was graded 2. Edema of the optic disks, irregularity of the caliber of the retinal arteries, exudates and hemorrhages were present. A grandparent had died of a stroke.

CASE 2.—A white housewife, aged 54, first noted general weakness. Other symptoms were impaired vision and a burning feeling in the feet and edema. Significant findings on physical examination were infected teeth, an enlarged heart and edema of the feet. Later paresthesia of the right side of the body developed. Previous illnesses included pertussis, scarlatina and a condition which probably was rheumatic fever. Sclerosis of the peripheral arteries was graded 2. Edema of the optic disks, sclerosis of the retinal arteries, hemorrhages and exudates were present. The patient's father had died of a stroke.

CASE 3.—A white housewife, aged 42, first noted anasarca. Other symptoms were headache, orthopnea and nocturia. Significant findings on physical examination were an enlarged heart, pericardial friction rub, ascites and edema. Later

35. Russel, Dorothy: A Classification of Bright's Disease, Medical Research Council, Special Report, Series no. 142, London, His Majesty's Stationery Office, 1929.

36. Aschoff, Ludwig: The Pathogenesis of the Contracted Kidney, Arch. Int. Med. **12**:723 (Dec.) 1913.

37. Braasch, W.: Ueber die klinischen Erscheinungen bei langendauernder Anurie, Deutsches Arch. f. klin. Med. **103**:488 (Aug.) 1911.

progressive dyspnea appeared. Previous illnesses included typhoid fever, tonsillitis and influenza. Sclerosis of the peripheral arteries was graded 1. Severe neuroretinitis, secondary optic atrophy, retinal arteriosclerosis, thrombosis of the retinal veins, exudates and hemorrhages were present. No history of a familial tendency to disease was obtained.

CASE 4.—A white farmer, aged 46, first noted edema. Other symptoms were orthopnea, nocturia and dyspnea. Significant findings on physical examination were emaciation, infected tonsils, ascites and râles in the lower part of the thorax. Later dyspnea progressed and breathing became irregular. Previous illnesses included influenza, jaundice and cholecystitis. Sclerosis of the peripheral arteries was graded 2. Moderate neuroretinitis and moderate sclerosis of the retinal arteries were present. Each of the patient's parents had died of a stroke. The effect of mercury possibly entered into this case. The patient used mild mercurous chloride for a cathartic. He also drank tea and coffee in large amounts.

CASE 5.—A white grain-buyer, aged 62, first noted occipital pain. Other symptoms were loss of memory, dyspnea, general weakness, edema and failing vision. Significant findings on physical examination were restlessness and presystolic and postsystolic cardiac murmur. Later the condition progressed rapidly. There was no history of previous illnesses. Sclerosis of the peripheral arteries was graded 4. Neuroretinitis, a few retinal hemorrhages and cotton-wool and star-shaped exudates were present. The patient's father had died of tuberculosis, and his mother of arteriosclerosis.

CASE 6.—A Negress, a housewife, aged 44, first noted asthmatic attacks. Other symptoms were dyspnea and a productive cough. Significant findings on physical examination were infected tonsils and râles in the lower part of the thorax. Orthopnea developed later. Previous illnesses included pneumonia, gonorrhea and tonsillitis. Sclerosis of the peripheral arteries was graded 1. Neuroretinitis was present.

CASE 7.—A white laborer, aged 40, first noted spells of choking. Other symptoms were pain in the right lower part of the back. Significant findings on physical examination were an enlarged heart and gallop rhythm. Later progressive dyspnea developed. The patient had previously had diphtheria. Sclerosis of the peripheral arteries was graded 3. Neuroretinitis, sclerosis of the retinal arteries and exudates were present. The patient used coffee and tobacco.

CASE 8.—A white railway conductor, aged 44, first noted pain in the upper part of the abdomen. Other symptoms were dyspnea, orthopnea, nocturia, headache and nausea. Significant findings on physical examination were pallor, dyspnea, râles over the lower part of the thorax and an enlarged, tender liver. Later the condition became rapidly worse. Previously, the patient had had renal colic. Sclerosis of the peripheral arteries was graded 1. There were edema of the disks (1 diopter) and sclerosis of the retinal arteries, grade 3, with distinct retinitis. The patient's mother had died of a stroke, and his brother had heart trouble. The patient used tea and coffee to excess.

CASE 9.—A white farmer, aged 39, first noted headache. Other symptoms were nocturia, impaired vision, loss of weight and orthopnea. The significant findings on physical examination were an enlarged heart and an enlarged liver. Later the condition became rapidly worse. Previously the patient had had tonsillitis. Sclerosis of the peripheral arteries was graded 1. Hyperemia and edema of the optic disks and sclerosis of the retinal arteries were present. The patient's

father had died of a stroke, and the patient's wife had died of tuberculosis. The patient used alcohol, tea and tobacco in moderation.

CASE 10.—A white truck driver, aged 23, first noted paralysis of the right side of the body. Other symptoms were headache and weakness. The significant finding on physical examination was weakness of the right side. The patient died suddenly, one year after the examination. Previous illnesses included appendicitis and syphilis. Sclerosis of the peripheral arteries was graded 1. Marked edema of the optic disks and constriction of the retinal arteries were present. No history was obtained of a familial tendency to disease. The patient had been given arsenic.

CASE 11.—A white farmer, aged 48, first noted headache. Other symptoms were nocturia and orthopnea. On physical examination, the only significant finding was pericardial friction rub. Later, steadily and rapidly, the condition became worse. Previous illnesses included pneumonia and rheumatism. Sclerosis of the peripheral arteries was graded 4. Edema of the optic disks and sclerosis of the retinal arteries were present.

CASE 12.—A white man, a government official, aged 50, first noted general fatigue. Other symptoms were dyspnea and headache. On physical examination the only significant finding was precordial murmur. Later the headache became increasingly severe. Sclerosis of the peripheral arteries was graded 2. Hyperemia and edema of the optic disks and sclerosis of the retinal arteries were present. The patient's father and two brothers had died of a stroke.

CASE 13.—A white farmer, aged 72, first noted blindness of the right eye. Other symptoms were dizziness, dyspnea and polyuria. On physical examination, significant findings were infected teeth and enlargement of the prostate gland. The condition rapidly became worse. Previous illnesses included influenza and intestinal hemorrhages. Sclerosis of the peripheral arteries was graded from 1 to 2. Sclerosis of the retinal arteries, graded from 2 to 3, edema of the optic disks, hemorrhages and exudates were present. The patient's father had died of a disease of the bladder; one brother had died of stroke and another of tuberculosis.

CASE 14.—A white housewife, aged 57, had a nervous breakdown as the first evidence of disease. Other symptoms were palpitation, dyspnea, nocturia, precordial pain and headache. The significant findings on physical examination were enlargement of the heart and thyroid gland and systolic murmur. The condition rapidly became worse. Previous illnesses included influenza and tonsillitis. Sclerosis of the peripheral arteries was graded 3. Edema of the optic disks, sclerosis of the retinal arteries, hemorrhages and exudates were present. The patient's father had died of paralysis.

CASE 15.—A white man, a factory worker, aged 24, first noted impairment of vision. Other symptoms were headache, nocturia, edema, epistaxis and vomiting. Significant findings on physical examination were irregular breathing and systolic cardiac murmur. Later the dyspnea increased. Previous illnesses included appendicitis, tonsillitis and acute nephritis with edema. Sclerosis of the peripheral arteries was graded 2. Edema of the optic disks, constriction of the retinal arteries and retinitis were present.

CASE 16.—A white man, a clothing worker, first noted generalized weakness. Other symptoms were blurring of vision, dyspnea, nocturia and nausea. Physical examination disclosed nothing of note. Right hemiplegia developed later. Previous illnesses included scarlatina, pleurisy, malaria, typhoid fever, influenza and tonsil-

litis. Sclerosis of the peripheral arteries was graded 1. Hyperemia and edema of the optic disks and retinitis were present. The patient's grandmother had died of apoplexy.

CASE 17.—A white housewife, aged 22, first noted gastric trouble. Other symptoms were backache, loss of weight and nocturia. Significant findings on physical examination were purpuric areas. A week later the patient became unconscious; she died in coma four days afterward. Previous illnesses included measles and typhoid fever. Sclerosis of the peripheral arteries was graded 2. Edema of the optic disks, constriction of the retinal arteries and hemorrhages and exudates were present. The patient's grandmother had died of diabetes. The patient had had three miscarriages.

CASE 18.—A white man, aged 44, first noted headache and vomiting. On physical examination the only significant finding was pulmonary edema. Severe neuroretinitis and sclerosis of the retinal arteries were present. The patient died within two days after his admission to the hospital.

CASE 19.—A white farmer, aged 39, first noted headache. Other symptoms were loss of vision, dyspnea and vomiting. On physical examination, significant findings were infected teeth, râles in the lower part of the thorax and enlargement of the liver. Later the dyspnea increased. The patient had previously had scarlatina. Sclerosis of the peripheral arteries was graded 3. Edema of the optic disks, sclerosis of the retinal arteries and retinitis were present. One living brother of the patient had hypertension.

CASE 20.—A white farmer, aged 39, first noted pains in the neck. Other symptoms were irregular fever, pains in the legs, weakness and numbness of the left hand, nocturia and edema. Significant findings on physical examination were epigastric tenderness, atrophy of the muscles, loss of tendon reflexes and enlargement of the liver. Later, mastitis, increase in fever and progressive weakness developed. Previous illnesses included tonsillitis and gonorrhea. Sclerosis of the peripheral arteries was graded from 0 to 1. The optic disks were hyperemic and exudates were present. The possible effect of lead and of arsenic had to be considered in this case. The patient used tobacco and alcohol and drank large amounts of tea and coffee.

CASE 21.—A white man, a postal clerk, aged 39, first noted headache. Other symptoms were insomnia, retrosternal pain, dyspnea, mental confusion and dimness of vision. Significant findings on physical examination were râles over the bases of the lungs and systolic cardiac murmurs. The patient previously had had tonsillitis. His death occurred a few days after registration. Neuroretinitis and sclerosis of the retinal arteries were present. The patient's father had died of tuberculosis and one living brother had heart disease.

CASE 22.—A white plumber, aged 29, first noted cramping pain in the left portion of the abdomen. Other symptoms were anginal pain, visual scotoma, blurring of vision and headache. Significant findings on physical examination were infected teeth and gallop rhythm. The condition became rapidly worse. The patient previously had had tonsillitis. Constriction of the retinal arteries, hyperemia and edema of the optic disks, exudates and hemorrhages were present. The patient's mother, who was living, had high blood pressure; his father had died of a stroke. The possible effect of lead had to be considered in this case.

CASE 23.—A white farmer, aged 56, first noted headache. Other symptoms were nocturia, nausea and vomiting. Significant findings on physical examination

were infected teeth and tonsils and enlargement of the heart, liver and prostate gland. Later, urinary retention developed, and the condition became rapidly worse. Previously the patient had had influenza. Sclerosis of the peripheral arteries was graded 1. Edema of the optic disks, retinitis and sclerosis of the retinal arteries were present. One brother had had tuberculosis; two living sisters had hypertension. Suprapubic cystostomy was performed.

CASE 24.—A white man, a real estate dealer, aged 41, first noted mild fatigue. Other symptoms were cough, nausea, vomiting, edema and dyspnea. Significant findings on physical examination were infected tonsils and enlargement of the heart and liver. Later, vomiting progressively increased in severity, and coma appeared. Previously the patient had had tonsillitis. Sclerosis of the peripheral arteries was graded 2. Edema of the optic disks, retinitis and thrombosis of the retinal veins were present. One living brother had tuberculosis.

CASE 25.—A white, road-building contractor, aged 37, first noted transient hematuria. Other symptoms were headache, colicky abdominal pain, failing vision, nocturia and cough. Significant findings on physical examination were infected teeth and enlargement of the heart. Later, edema, pericarditis and pneumonia developed. Previously the patient had had gonorrhea. Sclerosis of the peripheral arteries was graded 2. Edema of the optic disks, sclerosis of the retinal arteries and retinitis were present. The patient's mother, who was living, had heart trouble. The man used tobacco to excess.

CASE 26.—A white automobile dealer first noted slight weakness. Other symptoms were impaired vision, nocturia and mental confusion. Significant findings on physical examination were dry, red skin, otitis media, infected tonsils, an enlarged heart, edema and twitching of the muscles. Later, progressive dyspnea and edema developed. Previously the patient had had tonsillitis. Sclerosis of the peripheral arteries was graded 3. Edema of the optic disks, sclerosis of the retinal arteries, hemorrhages and exudates were present. The possible effect of arsenic must be considered in this case. The patient's wife had had two miscarriages.

CASE 27.—A white housewife, aged 51, first noted precordial pain. Other symptoms were headache, fatigue, vomiting and impaired vision. Significant findings on physical examination were enlargement of the heart, pericardial friction rub and consolidation of the bases of the lungs. Later, progressive dyspnea developed. Previously, the patient had had influenza. Sclerosis of the peripheral arteries was graded 3. Edema of the optic disks, constricted retinal arteries and retinitis were present.

SUMMARY

In a group of cases of malignant hypertension the findings on examination of microscopic sections consisted in diffuse changes involving glomeruli, tubules, arterioles, arteries and interstitial tissue. The most prominent changes occurred in the arterioles; they consisted in extreme narrowing of the lumen, apparent increase in the numbers of endothelial cells, subendothelial fatty and hyaline degeneration, apparent thickening of the tunica media and an increased amount of connective tissue, chiefly in the tunica adventitia. The ratios of the wall to the lumen of the renal arterioles were markedly reduced. The kidneys were not markedly or uniformly decreased in size.

CHANGES OF THE DIGESTIVE TRACT IN UREMIA

A PATHOLOGIC ANATOMIC STUDY

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Although the gastro-intestinal manifestations of uremia have attracted much attention and numerous contributions deal with their symptomatology, the literature contains but few systematic studies of the underlying pathologic-anatomic changes. The severe necrotizing and ulcerative lesions of the intestine especially are of great interest and have caused much controversy as to their frequency and pathogenesis. While some authors consider a dysentery-like inflammation of the colon and, partially, also of the ileum as one of the most characteristic post-mortem observations in uremia, Siegmund,[1] in a recent review on the subject, came to the conclusion that the severe changes are rare. This is in agreement with statements found in the older literature (Pineau,[2] Fédou,[3] Fischer [4] and others). Working in Kundrat's institute, Fischer found ulceration of the colon in only 4 of 17 cases of uremia. The majority of the patients showed only a swelling of the mucosa with superficial, microscopic areas of necrosis. The blood vessels of the submucosa were dilated, and the mucosa contained hemorrhages. The hemorrhagic character of the uremic lesions of the intestine has also been stressed by French investigators (Mathieu and Roux [5] and others). Siegmund described as the most common intestinal observation in uremia a diffuse edema of the mucosa with pseudomelanotic pigmenta-

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1. Siegmund, H., Einfache Entzündungen des Darmrohres, in Henke, F., and Lubarsch, O.: Handbuch der speziellen pathologischen Anatomie, Berlin, Julius Springer, 1929, vol. 4, pt. 3, p. 261.

2. Pineau, M.: Des hémorragies gastro-intestinales d'origine urémique, Thèse de Paris, 1899.

3. Fédou, A.: Contribution à l'étude des hémorragies intestinales au cours de l'urémie, Thèse de Toulouse, 1899.

4. Fischer, J.: Zur Kenntnis der Darmaffektionen bei Nephritis und Uraemie, Virchows Arch. f. path. Anat. **134**:380, 1893.

5. Mathieu, A., and Roux, J.: Sur un cas d'ulcérations urémiques de l'estomac et de l'intestin grêle, Arch. gén. de méd. **7**:14, 1902.

tion. The majority of the reports on uremic necrosis and ulceration of the intestine are based on the study of a single case or of a few cases only (Chiari,[6] Siegmund, Würth [7] and others). Pilliet,[8] Lancereaux,[8] Mathieu and Roux [5] and Lubarsch [9] referred to uremic changes in the stomach.

The attempts to explain the uremic lesions of the gastro-intestinal tract center about the compensatory elimination through the stomach and intestine of metabolic waste products which the kidneys have failed to excrete. In 1859, Treitz [10] formulated a theory which, though refuted by some authors, has held sway up to the present time. According to him the urea which is excreted through the glands of the intestinal mucosa in uremia is broken up in the lumen of the intestine into ammonia and carbonic acid. Ammonium carbonate, which exerts a caustic action on the mucosa, is formed. The experimental production of severe lesions of the intestine by the oral administration of ammonia water seemed to support Treitz's explanation. Hlava [11] was the first to attack the theory of Treitz, stressing the importance of a primary thrombosis of the small vessels of the intestinal mucosa. Fischer was not able to confirm Hlava's interpretation and considered the thrombi secondary to the necrosis and ulceration. Fischer assumed that the disturbed renal function led to an enterocolitis which, in some instances, became so severe as to cause necrosis and ulceration. He did not, however, explain the relations between the enterocolitis and the renal insufficiency. Mathieu and Roux considered the possibility of bacterial toxins as a potent factor in causing the severe intestinal changes. They pointed to the enormous dilatation of the venules and capillaries in the region of the ulcerations and suggested that this dilatation might diminish the vitality of the tissue. According to Pineau several factors act together to bring about the uremic necrosis and ulceration. These factors are: alteration of the blood vessels and perivascular tissue, irritation of the nerves and increase of the blood pressure. The significance

6. Chiari, H.: Ein Beitrag zur Lehre von der Uraemie, Verhandl. d. deutsch. path. Gesellsch. **15**:207, 1912.

7. Würth, W.: Ueber die Bedeutung der Arteriolensklerose für die Entstehung uraemischer Nekrosen, Virchows Arch. f. path. Anat. **284**:175, 1932.

8. Quoted by Konjetzny, G. E., in Henke, F., and Lubarsch, O.: Handbuch der speziellen pathologischen Anatomie, Berlin, Julius Springer, 1928, vol. 4, pt, 2, p. 934.

9. Lubarsch, O.: Pathologische Anatomie und Histologie der entzündlichen Erkrankungen des Magens, Verhandl. 6. Tagung der Gesellschaft f. Stoffwechsel u. Verdauungskrankheiten, Berlin, 1926.

10. Treitz: Ueber uraemische Darmaffektionen, Vrtljschr. f. prakt. Heilk. **64**: 143, 1859.

11. Hlava, quoted by Fischer.[4]

of the high blood pressure has also been emphasized by Lemierre [12] and by Bensaude, Cain and Antoine.[13] In 1923 Leyrat [14] again referred to the urea as causing the uremic ulcerations of the intestine. Having produced a uremic-like condition in dogs by the slow intravenous injection of large amounts of urea, Streicher [15] observed what he called a marked enteritis and congestion of the intestinal mucosa. From his illustration one obtains the impression that the mucosa was hemorrhagic rather than congested. Microscopic observations of the intestine are not given by Streicher.

In 1 case of chronic glomerulonephritis and in 3 cases of malignant nephrosclerosis with necrotizing lesions in the intestine Siegmund found arteriolonecrosis in the submucosa; this he considered as essential in causing the necrosis of the mucosa by interfering with the blood supply. Würth observed similar severe arteriolar changes in 1 case of arteriolosclerotic contracted kidney with focal areas of necrosis and ulceration in the large intestine. In 2 other cases of uremia, 1 of which showed extensive necrosis of the mucosa of the esophagus, stomach, pharynx and small and large intestine Würth, however, failed to find the arteriolar necrosis of the submucosa and preferred, therefore, the old theory of a toxic cause to Siegmund's theory of vascular origin.

Volhard,[16] who distinguished between acute eclamptic pseudo-uremia, chronic pseudo-uremia and true chronic uremia, classified the lesions of the digestive tract with the manifestations of the true uremia. The true uremia results from the renal insufficiency and auto-intoxication, while the two forms of pseudo-uremia are vascular and not directly related to the breaking down of the function of the kidneys. Volhard stated that in true chronic uremia there is a great tendency to infectious processes as terminal complications, admitting that the toxic action of retained endogenous waste products cannot be completely disposed of in explaining the intestinal changes.

From the review of the literature it is apparent that many additional experimental, biochemical and morphologic studies are required before the question of the uremic lesions of the digestive tract can be considered settled. The chemical aspects of uremia have recently been

12. Lemierre, A., and Piédelièvre, E.: Les ulcérations gastro-intestinales urémiques, leur rapport avec l'azotémie, Gaz. d. hôp. **94**:1437, 1921.

13. Bensaude, R.; Cain, A., and Antoine, E.: Contribution à l'étude de la recto-colite hemorrhagique d'origine urémique, Ann. de méd. **7**:41, 1920.

14. Leyrat, L.: Pathogénie des ulcérations gastro-intestinales urémiques, Thèse de Paris, 1923.

15. Streicher, M.: Experimental Uremia-Uremic Enteritis, Arch. Int. Med. **42**:835 (Dec.) 1928.

16. Volhard, F.: Die Uraemie, in von Bergmann, G., and Staehlin, R.: Handbuch der inneren Medizin, Berlin, Julius Springer, 1931, vol. 6, pt. 1.

reviewed by Volhard, to whom we owe much for the better understanding of the complex problem of uremia, and who has carried a great step forward the conception inaugurated by the work of Ascoli and Widal. This article is devoted to the morphology of the uremic lesions of the digestive tract.

MATERIAL

The study is based on 136 consecutive cases of uremia which came to autopsy between Jan. 1, 1929, and April 1, 1933. According to the underlying renal lesion the cases are distributed as follows: acute glomerulonephritis, 13; subacute glomerulonephritis, 13; chronic glomerulonephritis, 31; malignant nephrosclerosis, 72; pyelonephritis, 5; polycystic kidneys, 2. The high incidence of malignant nephrosclerosis is due to the high percentage of Negroes. As pointed out by one of us (Dr. Jaffé [17]), malignant nephrosclerosis is common in the colored race.

MACROSCOPIC OBSERVATIONS

The macroscopic changes which the digestive tract presented in the 136 cases of uremia varied considerably in extent and intensity, and, in general, there seemed to be no parallelism between the severity of these changes and the duration of the uremic state. In describing the changes we shall start with the mild forms and then gradually proceed to the severe ones.

In 37 cases (27.1 per cent) the essential change consisted of a slight to moderate edema of the submucosa which chiefly affected the large intestine. The mucosa of the ileocecal valve and of the cecum was often injected, and the inner surface was covered with an increased amount of mucus. In the stomach the excess of mucus was sometimes marked. In a few instances the mucosa of the ileum was raised to circular folds, the crests of which were deeply injected. The content of the large intestine was usually formed.

In 72 cases (52.9 per cent) hemorrhages were found in the mucosa of the digestive tract. Figure 1 *A* illustrates the distribution of these hemorrhages. Though no part between the lower half of the esophagus and the anus was spared, the stomach, ileum, cecum and colon were most frequently affected. Thirty-eight cases showed only single, loosely scattered petechiae from the size of a pinhead to about 4 or 5 mm. in diameter. In 22 cases the hemorrhages were more marked, while in 11 they were extensive. In the latter cases the picture was very characteristic. The deep red mucosa was raised to thick folds which were formed by the edematous submucosa, and the hemorrhagic areas shining through the serosa could be seen from the outside of the intestine. The

17. Jaffé, R. H.: Hypertonie und maligne Nephrosclerose bei Negern, Centralbl. f. allg. Path. **55**:209, 1932.

intestinal content was bloody, dark reddish-brown or tarry and semi-liquid. In the milder cases the mucus which covered the inner surface of the mucosa was often stained with blood.

Whether single or diffuse, the hemorrhages undoubtedly preceded the pseudomembranous and ulcerative lesions to be discussed next. In many instances one could see in the center of a hemorrhagic area a fine veil-like and light grayish-brown membrane which could easily be wiped off, leaving a slightly roughened, shallow depression. These fine membranes appeared first in the region of the ileocecal valve and at the height of the folds.

In 27 cases (19.8 per cent) pseudomembranous and ulcerative changes were present. Their distribution is shown in figure 1 *B*. In

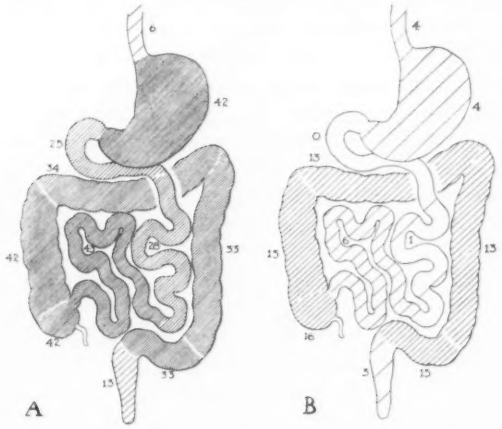

Fig. 1.—*A* shows the frequency of hemorrhages; *B*, the frequency of diphtheritic ulcerative changes in different parts of the intestinal tract. The figures refer to the number of cases.

3 cases the lower one third or one fourth of the esophagus was covered with an adherent, dirty grayish-brown and soft membrane which rested on a dark red hemorrhagic tissue. In 1 case the esophagus showed an irregular ulcer 4 by 3 cm. in diameter which was located just above the cardia. The floor of this ulcer was formed by a dirty grayish-brown material. In the group with uremic lesions of the stomach we do not include 1 case with an acute peptic ulcer and 3 cases with typical hemorrhagic erosions. We observed 1 instance of pseudomembranous gastritis. In the midportion of the lesser curvature for a distance of 3 cm. the mucosa of the stomach was transformed into an adherent, yellowish-gray membrane which was about 1 mm. thick and was sur-

rounded by a purplish-red zone. In the 3 other cases multiple small and shallow ulcers with sharp edges and a grayish-brown floor were found scattered in the fundus and prepyloric region.

In the intestine the changes were so pleomorphic that it would require much space to describe them in detail. They always showed intimate relations to hemorrhages and varied from a single raised necrotic plaque or a single ulcer a few millimeters in diameter to extensive dirty grayish-brown or greenish-brown membranes and large confluent ulcers. The ulcers were irregular with geographic outlines and indented edges that were not undermined. The floor was formed by the submucosa or muscularis propria and was usually covered with friable remnants of necrotic material. In the colon the ulcers occupied the height of the transverse and longitudinal folds. Ulcers and diphtheritic membranes were sometimes combined, and the picture was then indistinguishable from an acute bacillary dysentery. In 3 instances the ulcers of the intestine were associated with an early fibrinous peritonitis.

It is interesting to note that the duodenum was never affected by the pseudomembranous and ulcerative processes and that there was only 1 case of ulcerative jejunitis. In the French literature reference is occasionally made to a uremic ulcerative duodenitis, but Siegmund suggested that the lesions observed by the French authors were probably simple hemorrhagic erosions.

In the cases with the dysentery-like changes the content of the colon was liquid, often bloody, mixed with shreds of necrotic tissue and of offensive odor. The clinical picture was dominated by profuse and uncontrollable diarrhea. When only a few necrotic plaques or single ulcers were present, the intestinal symptoms were often less outspoken, and in some cases they were so slight that they did not attract the clinician's attention and were overshadowed by the nervous, respiratory and circulatory manifestations. Virchow made the statement that intestinal ulcerations may not cause diarrhea. The edematous and simple hemorrhagic changes in the intestine were sometimes found associated with persistent constipation. The variability of the intestinal symptoms in uremia has been stressed by Barrillon [18] and many others. According to Blanchet,[19] uremia is accompanied by diarrhea as often as by constipation. Volhard says that in rare instances the clinical and anatomic picture of uremia may closely resemble that of true dysentery. In reviewing the intestinal symptoms of 307 cases of chronic Bright's disease Fischer found diarrhea 84 times and constipation 45 times. Of 26 cases of uremia, 16 showed severe diarrhea.

18. Barrillon, Maurice: Contribution à l'étude de l'urémie digestive, Thèse de Paris, no. 68, 1897.

19. Blanchet, R.: Contribution à l'étude de l'urémie gastro-intestinale, l'urémie occlusive, Thèse de Paris, 1911.

Since pseudomembranous and ulcerative lesions of the gastro-intestinal tract in uremia are of grave significance, their early recognition is of great importance. This early recognition, however, is often rendered difficult because of the absence of characteristic symptoms. Anatomic observations suggest that the microscopic and chemical demonstration of blood in the feces should prove a valuable sign of the imminent danger of severe gastro-intestinal complications.

A question arises as to the relations between the type of renal lesion that causes the uremia and the intensity of the gastro-intestinal changes. Pseudomembranous and ulcerative processes were encountered most frequently in cases of uremia due to pyelonephritis (40 per cent), but since there were only 5 cases of pyelonephritis with uremia in our material the number is too small to permit us to draw any definite conclusions. Acute glomerulonephritis was second in frequency with 30.2 per cent. Subacute glomerulonephritis followed next with 23.0 per cent and chronic glomerulonephritis with 19.3 per cent. For malignant nephrosclerosis the corresponding figure was 16.6 per cent. It seems, therefore, that glomerulonephritis leads more frequently to necrosis and ulceration in the digestive tract than the vascular form of renal insufficiency. Further studies on a larger amount of material are necessary to show whether this statement is correct.

MICROSCOPIC OBSERVATIONS

In the mild forms of uremic intestinal changes histologic examination reveals a thickening of the submucosa and a dilatation of the veins of the basal venous plexus of the mucosa and especially of the submucosa. The thickening of the submucosa is due to an edematous loosening of the ground substance and, in many instances, also to an actual increase in connective tissue fibers. The crypts of the mucosa are dilated and filled with mucus and desquamated and degenerated epithelial cells. With the onset of the hemorrhages the congestion of the venules and veins becomes most marked, and there is an extreme stasis in the capillaries of the mucosa (fig. 2). In the veins of the submucosa the red cells are often so densely packed together that they form solid casts (fig. 3). The first hemorrhages appear in the basal parts of the mucosa and spread gradually to the inner surface. In the severe forms there is a complete hemorrhagic infarction of the mucosa. The crypts are filled with cellular débris and red blood cells, and the edema is most striking in the submucosa. In the stage of hemorrhagic infarction of the mucosa the venules of the submucosa show peripheral accumulation of the leukocytes and also leukodiapedesis (fig. 4). Proliferation of the local histiocytes and filling of the lymph vessels with

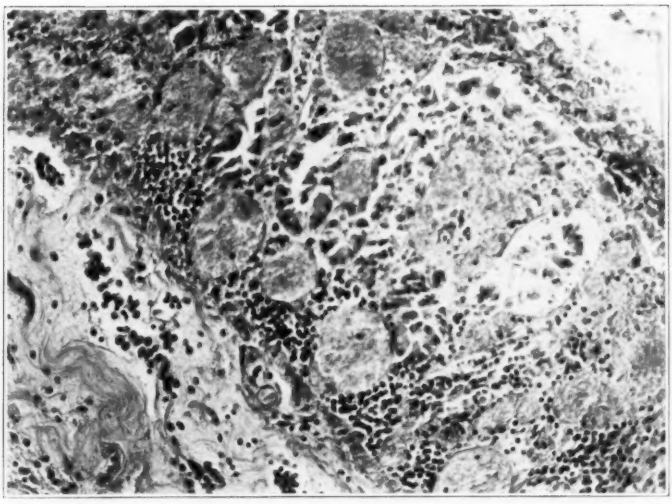

Fig. 2.—Section of the lower ileum showing marked engorgement of the deep venous plexus of the mucosa and numerous hemorrhages above the dilated venules. The submucosa is edematous. There is an increase in the number of local histiocytes with an accumulation of mononuclear cells in the lymph vessels. The patient was a colored man, aged 38, suffering from chronic glomerulonephritis with focal areas of cortical necrosis. The duration of the uremic symptoms was three weeks. Reduced from a magnification of × 300.

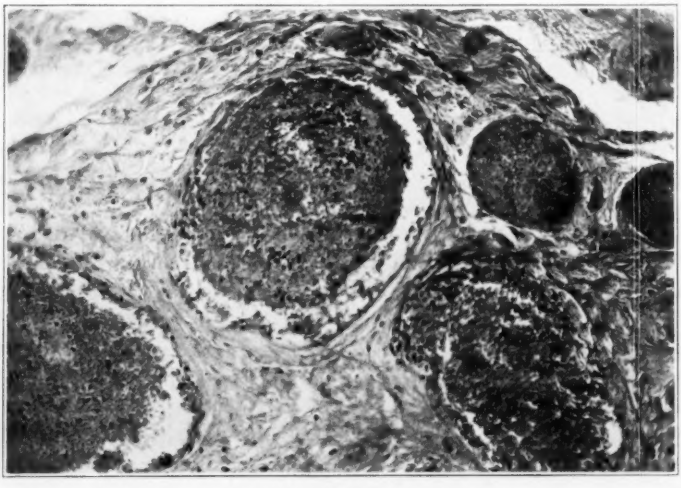

Fig. 3.—Section of the ascending colon illustrating the enormous dilatation of the veins of the submucosa. The patient was a white man, aged 44, with chronic glomerulonephritis. The duration of the uremic symptoms was one month. Reduced from a magnification of × 300.

Fig. 4.—Section of cecum. Note the hemorrhagic infarction of the mucosa and the enormous edema of the submucosa. The venules in the submucosa show a peripheral arrangement of the leukocytes and leukodiapedesis. The patient was a white man, aged 50, with subacute glomerulonephritis. The duration of uremic symptoms was three weeks. Reduced from a magnification of × 150.

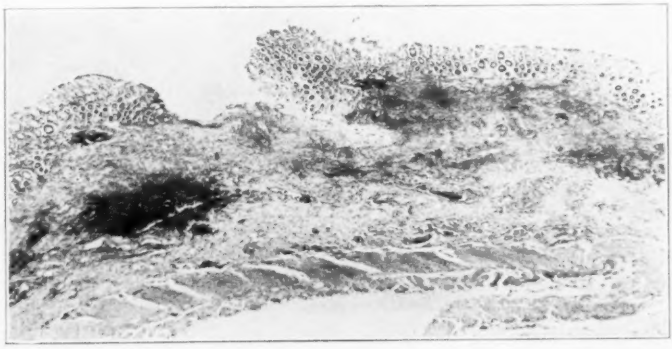

Fig. 5.—Section of the cecum showing a uremic ulcer. There are extensive hemorrhages in the floor and at the edges of the ulcer. The overhanging edge on the right side of the ulcer is an artefact due to shrinking. The patient was a colored man, aged 46, with malignant nephrosclerosis. The duration of uremic symptoms was one week. Reduced from a magnification of × 18.

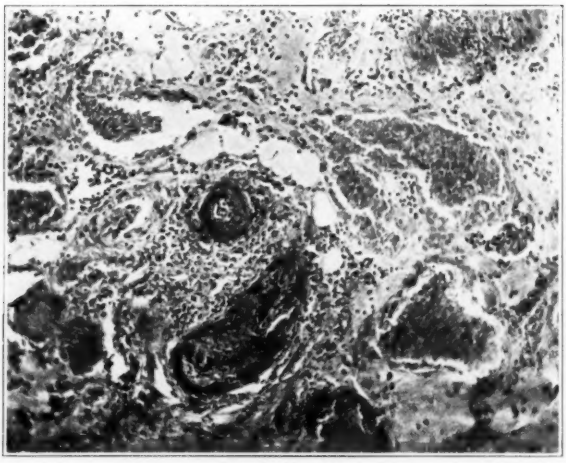

Fig. 6.—Necrotic arteriole surrounded by leukocytes in the submucosa. Severe pseudomembranous ileitis. A thrombosed small vein is seen near the necrotic arteriole. The mucosa above this area is completely necrotic. The patient was a white woman, aged 28, with malignant nephrosclerosis. The duration of uremic symptoms was twelve days; × 150.

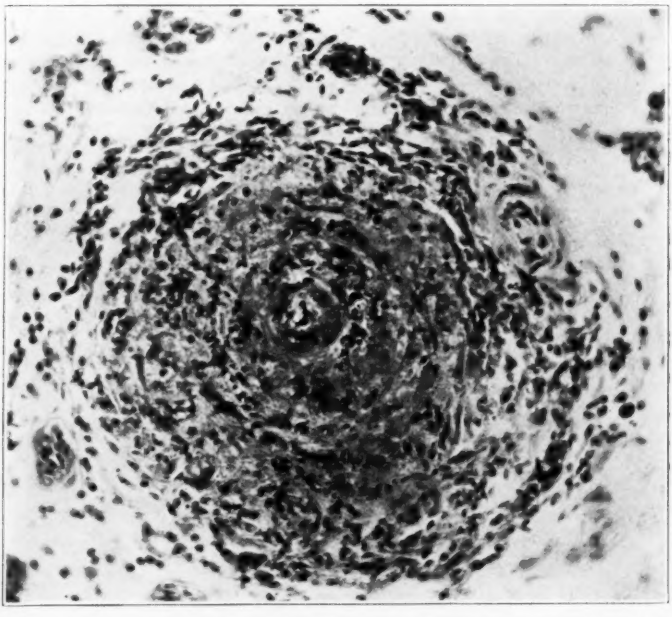

Fig. 7.—Necrotic arteriole surrounded and infiltrated by leukocytes in the submucosa of the ileum. The mucosa was necrotic, and the necrosis extended close to the arteriole. The patient was a colored man, aged 38, with chronic glomerulonephritis. The duration of uremic symptoms was two and one-half weeks; reduced from a magnification of × 500.

mononuclear cells add to the increased cellularity of the submucosa. On the free surface there is a thin layer of blood mixed with degenerating cells, threads of fibrin and clumps of bacteria.

In the state of diphtheritic inflammation the mucosa is completely necrotic, and the necrosis often extends into the submucosa. Dense clouds of bacteria populate the inner portion of the necrotic membranes underneath which one finds extravasations of blood and a varying degree of demarcating inflammation. In some cases this demarcating inflammation is rather insignificant. The veins about the area of necrosis are often occluded by thrombi.

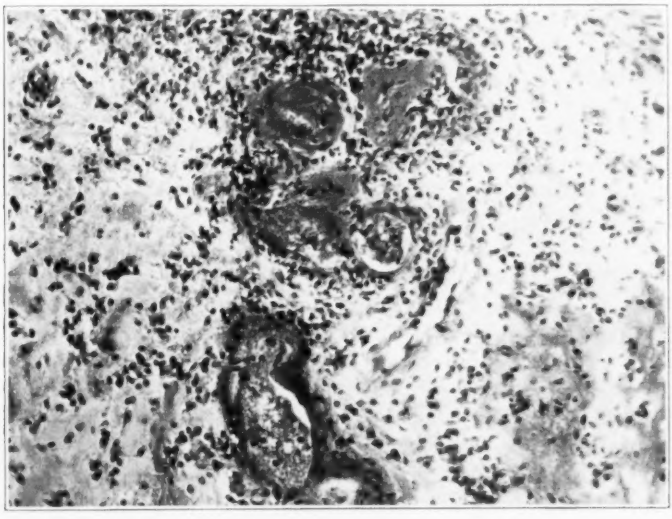

Fig. 8.—Arteriolar necrosis in the submucosa of the colon in a case of Flexner's dysentery. Reduced from a magnification of × 300.

The uremic ulcer of the intestine (fig. 5) has sloping edges. The floor exposes a layer of fibrinoid necrotic tissue with degenerating leukocytes. Hemorrhages in the floor and at the edges of the ulcer are of particular significance and, according to our experience, are more extensive than in any other form of intestinal ulceration.

As pointed out in the introductory review of the literature, Siegmund is inclined to associate the uremic ulceration and necrosis of the intestine with arteriolar changes. It is well known that in cases of hypertension the intestine may take part in the sclerotic changes of the arterioles, although they are not as common and as marked as in the kidney (Fahr). We found no arteriolar changes in 9 of our 27 cases of diphtheritic and ulcerative inflammation of the intestine. In 13 cases there

was a distinct arteriolosclerosis, and necrosis of the arterioles and small arteries of the submucosa was present in 5 cases (figs. 6 and 7). The necrosis affected both previously sclerotic and unchanged vessels. The vascular necrosis was always in close proximity to the necrosis of the mucosa and was never encountered during the congestive or hemorrhagic stage of the lesions. Thus, it is undoubtedly secondary. In this connection it may be recalled that arteriolar necrosis of the submucosa is quite common in bacillary dysentery (fig. 8). Furthermore, the necrosis is distinctly inflammatory, as shown by the leukocytic infiltration in and about the necrotic vessels (fig. 7) and, hence, different from the bland fibrinoid necrosis of the arterioles of the kidneys in cases of malignant nephrosclerosis.

COMMENT

In our material diphtheritic and ulcerative lesions of the digestive tract were third in frequency among the pathologic-anatomic manifestations of uremia, uridrosis being first with 32.3 per cent and fibrinous pericarditis second with 30.8 per cent. It is significant that fibrinous pericarditis was less common in the patients with severe gastro-intestinal changes than it was in those showing mild changes. Fibrinous pericarditis was present in only 25.9 per cent of the patients with diphtheritic ulcerative lesions, while it was observed in 32.1 per cent of those with edema and hemorrhages, which indicates that different factors are at work in causing the pericarditis and the intestinal necrosis.

We have reviewed the theories which deal with the pathogenesis of uremic necrosis and ulceration of the digestive tract. Siegmund's explanation has already been discarded on the basis of the microscopic observations. Our observations also do not support the old and often quoted theory of Treitz which is based on the compensatory elimination of urea through the glands of the stomach and intestine. When one divides the cases of uremia into two groups, one with and one without necrotic or ulcerative lesions of the gastro-intestinal tract, one observes practically no difference in the degree of retention of urea. The general average is slightly higher in the first than in the second group, the respective figures for urea nitrogen being 137 mg. and 120 mg. per hundred cubic centimeters of blood. The range of variation, however, is about the same, namely between 50 and 250 mg., and the extremely high values (above 200) are not more common in the first than in the second group. The relatively small number of cases and the wide range of variation of the urea content of the blood do not allow a satisfactory calculation of the standard variation for the group with intestinal necrosis and ulceration. But even without exact mathematical figures it can be safely stated that there is no parallelism between the severity of the gastro-intestinal changes and the retention of urea. What has

been said of the urea also holds true for the other substances which were determined in the blood, namely, creatinine, uric acid and indican. Nor were there any differences in the decrease of the carbon dioxide-combining power of the plasma. Determinations for xanthoprotein were not made on our patients. There is an additional important factor which speaks against the theory of excretion, namely, the occurrence of diphtheritic and ulcerative lesions in the esophagus and, especially, in the vagina, the evolution of which is identical with that of the intestinal changes. While the literature refers occasionally to the involvement of the esophagus, the changes in the vagina are hardly mentioned, although they are characteristic. In 8 (13.1 per cent) of our 61 female patients with uremia a diphtheritic or ulcerative colpitis was recorded. Many of the remaining 53 cases showed discrete or confluent hemorrhages in the vaginal mucosa. So far as the hypertension theory of Bensaude and Lemierre is concerned, an exceedingly high blood pressure did not seem to favor the development of pseudomembranes or ulcers.

Comparing the two schematic drawings in figure 1 which depict the frequency of the hemorrhages and diphtheritic and ulcerative changes, respectively, in the lower part of the esophagus, stomach and intestine, one observes an important difference. While the hemorrhages are equally common in the stomach, ileum and colon and are also frequently encountered in the duodenum and jejunum, the severe lesions reveal a distinct predilection for the ileum and colon. In other words, necrosis and ulceration occur chiefly where the intestinal content is rich in bacteria. The hemorrhagic areas of the esophagus become infected by the bacteria which are swallowed with the food, mechanical factors determining the selection of the lowermost portion. Mechanical factors are also instrumental in disposing the region of the ileocecal valve to necrosis and ulceration. There was only 1 instance of pseudomembranous inflammation in the stomach. The ulcers in the other 3 cases were somewhat different from typical hemorrhagic erosions, but since they were sharply punched out, they too were most likely peptic.

We believe, therefore, that the uremic necrosis and ulceration of the intestine are secondary to hemorrhages, as Mathieu and Roux suggested many years ago. The hemorrhages loosen the epithelial cover of the mucous membranes and decrease the vitality of the tissue. Where present, bacteria infect the hemorrhagic tissue, causing necrosis and ulceration. There is no indication for the elimination of chemical substances so strong as to produce necrosis. The hemorrhages in the digestive tract are a part of the hemorrhagic diathesis which is common in uremia and which leads to hemorrhages in many other organs, as for instance in the epicardium, lung, mucosa of the renal pelvis, urinary bladder,

uterus and vagina. Six of our patients showed so many petechiae of the skin that the diagnosis on admission suggested a blood dyscrasia. Morawitz [20] explained the hemorrhagic diathesis in uremia on the basis of the autointoxication. We do not know what substance acts on the vessels to make them permeable for the blood cells. Nor are we able to decide definitely whether this substance affects the vessels directly or indirectly by way of the vasomotor nerves in the sense of Ricker. The latter explanation appears to us more likely, since no anatomic alterations of the wall of the capillaries or small veins could be detected, and the extreme dilatation of the capillaries and small veins was in striking contrast to the narrow arterioles and small arteries. Thus, the histologic observations suggest that, similar to the chief manifestations of the acute eclamptic and chronic pseudo-uremia, the intestinal lesions of true uremia are the result of disturbances in the innervation of the terminal vascular bed. In the two forms of pseudo-uremia these disturbances affect mainly the central nervous system, leading to edema, focal rarefaction of the ganglion cells and, eventually, softening and hemorrhages. In true uremia they are more generalized, causing hemorrhages in many organs of the body (esophagus, ileum, colon and vagina), which, in the presence of bacteria, are followed by necrosis and ulceration.

SUMMARY

The study deals with the pathologic-anatomic changes of the digestive tract in uremia. The diphtheritic ulcerative processes which were encountered in 19.8 per cent of the 136 cases could be traced to localized circulatory disturbances. The earliest changes consist of capillary hyperemia of the mucosa, increased production of mucus and dilatation of the small veins of the submucosa. The increased permeability which is associated with the extreme widening of the small blood vessels leads first to edema and later to hemorrhages. Bacteria from the intestinal content settle in the devitalized hemorrhagic areas of the mucosa of the intestine and cause fibrinous exudation and necrosis. The necrotic parts are sequestrated, and ulcers are formed.

Attention is called to the occurrence of a pseudomembranous ulcerative colpitis in uremia, the pathogenesis of which is identical with that of the intestinal lesions.

20. Morawitz, P.: Verhandl. d. deutsch. path. Gesellsch. **25**:32, 1930.

EFFECT OF ARTERIOSCLEROSIS AND BENIGN AND MALIGNANT HYPERTENSION ON THE AREA OF HISTAMINE FLARES

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AND
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CLEVELAND

The syndrome of malignant hypertension, as described by Keith and his associates,[1] is characterized by severe arterial hypertension, neuroretinitis, a progressive course and a uniformly poor prognosis. The condition usually represents the final stage of benign essential hypertension, but occasionally appears to be of the malignant type from the onset. The neuroretinitis varies in severity from mild to extreme in different cases and in all but the final stage is characterized by the invariable presence of edema of the disks, with edema of the surrounding retina. This feature is often out of proportion to the other retinal changes, such as hemorrhagic areas, cotton-wool exudates and sclerosis of the retinal arteries. Renal function frequently is normal or only slightly reduced at the time the condition is first recognized. The erythrocyte count and hemoglobin content of the blood are seldom more than slightly diminished. Death usually occurs within two years after the diagnosis is made and may be result of cerebral hemorrhage, congestive myocardial failure, renal insufficiency or a combination of these causes.

The differentiation of typical cases of benign and malignant hypertension is comparatively simple and is based primarily on the results of ophthalmoscopic examination. There is a group of cases, however, which cannot be placed in either the benign or the malignant class. Ophthalmoscopic examination reveals more extensive changes, in the form of retinal sclerosis, exudates and hemorrhagic areas, than are present in patients with benign hypertension, and yet, because of the absence of edema of the disks, the condition cannot be classified as malignant hypertension. Some of these undoubtedly are cases of early malignant hypertension, while others represent severe grades of the benign form. In the present study these cases have been grouped together and labeled

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From the Cleveland Clinic.

1. (*a*) Wagener, H. P., and Keith, N. M.: Cases of Marked Hypertension, Adequate Renal Function and Neuroretinitis, Arch. Int. Med. **34**:374 (Sept.) 1924. (*b*) Keith, N. M.; Wagener, H. P., and Kernohan, J. W.: The Syndrome of Malignant Hypertension, ibid. **41**:141 (Feb.) 1928.

hypertension of intermediate grade. Kernohan, Anderson and Keith [2] employed a similar classification.

Pathologic studies of the arterioles of voluntary muscle obtained at biopsy and of the arterioles of various organs at necropsy were made by Kernohan, Anderson and Keith [2] in patients with hypertension of the benign, intermediate and malignant types. They observed that in benign hypertension the arterioles may be entirely normal or may show moderate lesions, while in the intermediate and malignant types more advanced changes are the rule. The lesions consist of hypertrophy of the media, proliferation of the intima and marked reduction in the ratio of the wall to the lumen. The character and widespread distribution of these changes in the arterioles and the probability that the arterioles are also in a state of greatly increased tone [3] suggested that patients with hypertension of the intermediate and malignant types might show alterations in the response of the cutaneous vessels to histamine.

Sir Thomas Lewis [4] observed that when a solution of histamine acid phosphate is placed on the skin of normal persons and punctured into the epidermis with a fine needle, the ensuing reaction consists of three distinct phases. There first appears a reddish-purple spot about the site of the puncture. This is surrounded within a minute or less by a bright flare, and finally, the original reddish-purple spot is covered by a wheal. The entire reaction reaches its maximum development in from three to five minutes. After extensive studies Lewis concluded that the purplish spot about the site of puncture results from local dilatation of the minute vessels of the skin (terminal arterioles, capillaries, collecting venules and subpapillary venous plexus), and that the wheal is due to increased permeability of the walls of these vessels. The flare, on the other hand, is the result of widespread dilatation of the neighboring strong arterioles (arched arterioles), and is brought about through a local nerve reflex (axon reflex). Dilatation of the strong arterioles causes passive engorgement of the minute vessels of the skin, and it is to the congestion of these vessels that the arterial color of the histamine flare is due.

The available evidence cited earlier indicates the presence of a disturbed state of the arterioles in patients with essential hypertension. As the flare is more directly related to the condition of the arterioles than are the other two phases of the histamine reaction, it seemed probable that if different grades of essential hypertension produced quantitative

2. Kernohan, J. W.; Anderson, E. W., and Keith, N. M.: The Arterioles in Cases of Hypertension, Arch. Int. Med. **44**:395 (Sept.) 1929.

3. Volhard, F.: Der arterielle Hochdruck, Verhandl. d. deutsch. Gesellsch. f. inn. Med. **35**:134, 1923.

4. Lewis, T.: The Blood Vessels of the Human Skin and Their Responses, London, Shaw & Sons, Ltd., 1927.

differences in the response to histamine, the alterations could be detected best by observations on the area of the flare. Actual measurements of the area of histamine flares do not appear to have been made, and for this reason control observations in normal persons were necessary. In addition, because earlier investigators [5] recorded delayed or reduced responses to histamine in patients with arteriosclerosis, it seemed desirable to include in the present study measurements of the area of the flare in patients with arteriosclerosis and normal blood pressure.

METHODS OF STUDY

The technic of puncturing the skin through a drop of histamine solution was discarded in favor of the intradermal injection of a measured amount of the drug. With the latter procedure larger flares may be obtained, and these flares, as a rule, are less variable in size than are those produced by the puncture method. All observations were made at ordinary room temperature, with the patient in the recumbent position and with the arms supported at the level of the right auricle. The skin of the flexor surface of the midforearm was swabbed gently with alcohol and allowed to dry. Approximately 0.02 cc. of a 1:2,000 solution of histamine dihydrochloride containing 0.5 per cent of chlorbutanol as a preservative was then injected into the superficial layers of the skin with a tuberculin syringe and a 26 gage hypodermic needle. The development of the flare was observed carefully, and at the end of five minutes or as soon thereafter as the reaction was complete the borders of the flare were outlined with ink and traced on thin copy paper. The intensity of the color was noted. The surface area of the flare was measured subsequently by retracing the outline from the copy paper to thin lead foil of uniform thickness and uniform weight per square centimeter. The pattern on the foil was cut out and weighed, and the area of the flare was calculated from the known weight of the foil per unit of area.

Observations were made on both forearms in each patient studied, and, in approximately one half of the persons the test was repeated on one or more occasions. In each subject the average of all measurements on both forearms was taken as the final area of the flare. On rare occasions, and apparently as the result of the escape of the histamine solution into the lymphatic system of the skin, wheals were formed with long projecting tongues instead of the usual fairly regular outline. These wheals were accompanied by abnormally large flares, and because the form of the wheals indicated an abnormal distribution of the stimulus, reactions of this kind were not included in computing the results.

All persons subjected to the test had a normal oral temperature at the time the observations were made, and none presented evidence of congestive myocardial failure. Routine blood counts and urinalyses were made in all subjects, and in the patients with hypertension the renal function was measured by the urea clearance

5. Starr, I., Jr.: Studies on the Circulation of the Feet in Diabetes Mellitus With and Without Gangrene, Am. J. M. Sc. **180**:149, 1930. Caldwell, J. M., Jr., and Mayo, J. G.: Cutaneous Reactions to Histamine: Reactions in Occlusive and Spastic Vascular Disease and in Chronic Infectious Arthritis, Arch. Int. Med. **47**: 403 (March) 1931. de Takáts, G.: The Cutaneous Histamine Reaction as a Test for Collateral Circulation in the Extremities, ibid. **48**:769 (Nov.) 1931.

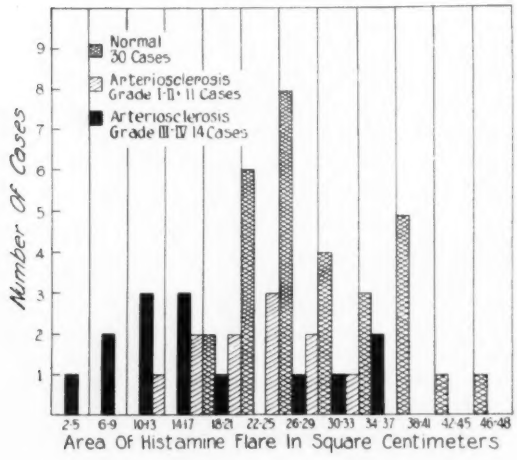

Chart 1.—Comparative distribution of the areas of the histamine flare in normal persons and in patients with arteriosclerosis and normal blood pressure.

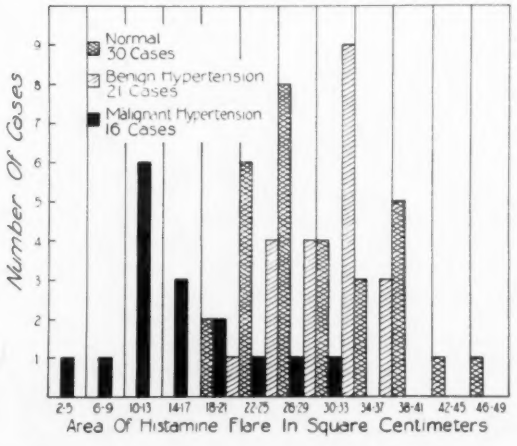

Chart 2.—Comparative distribution of the areas of the histamine flare in normal persons and in patients with benign and malignant hypertension.

test.[6] Care was exercised to exclude possible instances of chronic glomerulonephritis from the series of cases of benign, intermediate and malignant hypertension.

RESULTS

The area of the flare produced by the intradermal injection of histamine was measured in five groups: (1) thirty normal persons, (2) twenty-five patients with arteriosclerosis and normal blood pressure, (3) twenty-one patients with essential hypertension of the benign type, (4) eleven patients with hypertension of the intermediate grade and (5) sixteen patients with malignant hypertension.

Normal Conditions.—The normal persons were between 18 and 58 years of age. The blood pressure was within the limits of normal in all, and in none was there palpable thickening of the radial or brachial arteries. The area of the histamine flare ranged from 18 to 48 sq. cm., with an average value of 31 sq. cm. An area of less than 25 sq. cm. was recorded in only six instances. In several persons there was a considerable variation in the area of the flare on the two forearms and in the size on the same arm at different times. In no instance, however, was an abnormally small flare observed.

Arteriosclerosis and Normal Blood Pressure.—Eleven patients between the ages of 48 and 75 years had slight or moderate peripheral arteriosclerosis and normal blood pressure. In none of these did the history or physical findings, including the results of ophthalmoscopic examination, suggest that hypertension had been present in the past. The color of the histamine flare was normal in all instances but one. There was a tendency, however, toward a slight diminution in the size of the flare. The area was less than 25 sq. cm. in seven of the eleven patients, but in only three was it smaller than the smallest recorded in a normal person. The average area for the entire group was 22 sq. cm.

Fourteen patients between the ages of 50 and 80 years had advanced arteriosclerosis and normal blood pressure. None presented evidence of having had hypertension in the past. The color of the histamine flare was paler than normal in five. Although the area varied in different persons from 3 to 36 sq. cm., a distinctly greater tendency toward flares of reduced size was observed than in the group with lesser degrees of arteriosclerosis. In nine of the fourteen patients the flare was smaller than the smallest recorded in a normal person. The average area for the entire group was 18 sq. cm.

Benign Hypertension.—The twenty-one patients with essential hypertension of the benign type were between the ages of 29 and 67

6. Möller, E.; McIntosh, J. F., and Van Slyke, D. D.: Studies of Urea Excretion: II. Relationship Between Urine Volume and the Rate of Urea Excretion by Normal Adults, J. Clin. Investigation **6**:427 (Dec.) 1928.

TABLE 1.—*Observations on Patients with Benign Hypertension*

No.	Age, Years	Sex	Blood Pressure		Duration of Hypertension, Years	Peripheral Arteriosclerosis, Grade	Fundus		Blood			Urine				Histamine Flare	
			Systolic, Mm. Hg	Diastolic, Mm. Hg			Retinitis	Sclerosis	Erythrocytes, Millions	Hemoglobin, per Cent	Urea, Mg.	Specific Gravity	Albumin	Casts	Urea Clearance, per Cent	Color	Area, Sq. Cm.
1	50	F	174	104	4+	0	0	Slight	5.6	84	24	1.022	0	0	145	Normal	30
2	54	M	170	106	Unknown	II	0	Slight	4.8	88	30	1.020	Trace	0	41	Normal	32
3	61	F	182	100	10+	II	0	Advanced	4.7	84	42	1.017	Trace	0	40	Normal	27
4	59	M	180	104	3	I	0	Moderate	5.0	104	30	1,020	0	0	41	Normal	31
5	29	F	170	110	4	0	0	Slight	4.8	87	30	1.020	Trace	0	81	Normal	26
6	63	M	230	124	5+	II	0	Slight	4.2	65	33	1.017	0	+	..	Normal	31
7	49	F	210	110	12+	I	0	Slight	4.5	60	27	1.026	Trace	0	72	Normal	20
8	38	F	196	126	12+	0	0	Slight	4.4	85	24	1.022	0	0	66	Normal	30
9	49	F	210	118	4—	I	H.*	Slight	4.6	80	30	1.020	Trace	+	76	Normal	35
10	55	F	184	94	Unknown	I	0	Slight	4.2	71	36	1.027	Trace	0	65	Normal	25
11	55	M	200	106	Unknown	I	0	Slight	5.1	97	..	1.024	0	0	..	Normal	22
12	58	M	160	96	7+	III	0	Slight	5.1	91	45	1.023	Trace	+	78	Normal	28
13	49	F	210	110	6+	II	0	Moderate	4.8	84	33	1.021	0	0	45	Normal	35
14	42	M	206	106	Unknown	II	0	Slight	4.0	61	42	1.030	0	0	69	Vivid	36
15	58	M	196	112	Unknown	II	H.*	Moderately advanced	4.9	84	24	1.022	Trace	0	141	Pale	32
16	45	F	196	116	4+	II	0	Slight	4.8	90	39	1.018	0	0	59	Normal	33
17	52	F	230	110	8+	I	0	Moderate	5.0	85	36	1.026	Trace	0	85	Pale	26
18	40	F	220	110	Unknown	I	0	Moderate	4.1	84	42	1.012	0	0	43	Normal	23
19	67	F	190	100	6—	I	0	Moderate	4.6	78	24	1.030	0	0	65	Normal	24
20	56	M	180	116	Unknown	II	0	Moderate	5.1	91	28	1.021	0	0	72	Normal	30
21	42	F	230	126	Unknown	I	0	Advanced	4.8	91	30	1.020	0	0	100	Normal	31
Average	51		196	110	.....				4.7	83	32	.....			73		29

* Few small hemorrhages.

years. The average blood pressure was 196 systolic and 100 diastolic. The duration of the hypertension in the patients in whom it could be estimated ranged from three to more than twelve years. Slight or moderate peripheral arteriosclerosis was usually present. Ophthalmoscopic examination revealed from slight to advanced sclerosis of the retinal vessels, but in no instance was there retinitis or papilledema. The color of the histamine flare was diminished in only two instances. The area of the flare was within the limits of normal in all, and the average area for the group was 29 sq. cm. A summary of the observations on patients with benign hypertension is presented in table 1.

Hypertension of the Intermediate Grade.—The eleven patients with essential hypertension of the intermediate grade were between the ages of 34 and 62 years. The average blood pressure was 210 systolic and 120 diastolic. The duration of the hypertension in the patients in whom it could be estimated varied from approximately one to eighteen years. From slight to moderately advanced peripheral arteriosclerosis was present in all. Ophthalmoscopic examination revealed from moderate to advanced sclerosis of the retinal vessels and from slight to advanced degrees of retinitis. In four patients the outline of the optic disks was hazy, but actual papilledema was not present. The color of the histamine flare was diminished in only two instances, but a well defined tendency toward reduction in area was observed. In only two of the eleven patients did the area exceed 25 sq. cm., while in four the flare was smaller than the smallest recorded in a normal subject. The average area for the entire group was 20 sq. cm. A summary of the observations is presented in table 2.

Malignant Hypertension.—The sixteen patients with malignant hypertension were between the ages of 26 and 66 years. The average blood pressure was 225 systolic and 130 diastolic. The duration of the hypertension in the patients in whom it could be estimated ranged from less than three years to eight years. A certain degree of peripheral arteriosclerosis was present in all the patients, but in only three was this of advanced grade. Edema of the optic disks and of the surrounding retina was present in all but one patient, in whom there was an extensive bilateral vitreous hemorrhage obscuring the disks. Exudates and hemorrhagic areas were noted in fourteen of the sixteen patients, but in many these changes were slight in comparison with the degree of neuroretinal edema. Sclerosis of the retinal vessels was an invariable finding, and usually was of moderate or advanced grade. Abnormally pale histamine flares were obtained in seven of the sixteen patients in this group. In eleven patients the area of the flare was less than the smallest observed in a normal subject, while in only three did it exceed 24 sq. cm. The average area for the entire group was 16 sq. cm., approximately

TABLE 2.—*Observations on Patients with Essential Hypertension of Intermediate Grade*

No.	Age, Years	Sex	Blood Pressure		Duration of Hypertension, Years	Peripheral Arteriosclerosis, Grade	Fundus		Blood			Urine				Histamine Flare	
			Systolic, Mm. Hg	Diastolic, Mm. Hg			Retinitis	Sclerosis	Erythrocytes, Millions	Hemoglobin, per Cent	Urea, Mg.	Specific Gravity	Albumin	Casts	Urea Clearance, per Cent	Color	Area, Sq. Cm.
1	55	F	230	120	3	I+	Slight	Moderately advanced	5.0	91	42	1.009	0	0	40	Normal	21
2	34	M	150	106	1½	II	Slight	Moderately advanced	5.1	91	39	1.015	0	0	96	Pale	20
3	53	F	220	112	Unknown	II+	Slight	Advanced	4.6	91	45	1.019	Trace	0	50	Normal	16
4	53	F	210	120	18	I	Slight	Moderate	4.5	84	33	1.008	Trace	0	25	Vivid	14
5	59	F	220	110	5	I	Moderately advanced	Moderately advanced	4.4	84	30	1.020	Trace	0	72	Normal	33
6	62	M	204	114	3+	III+	Slight	Advanced	4.6	97	45	1.023	Trace	0	74	Normal	20
7	58	M	200	120	Unknown	II	Moderately advanced*	Moderately advanced	4.9	81	45	1.025	Trace	+	54	Normal	26
8	46	F	180	98	1+	I	Slight*	Advanced	4.6	81	54	1.012	Trace	0	46	Normal	22
9	61	M	256	160	10+	III+	Slight*	Advanced	4.0	74	75	1.020	+	++	30	Pale	13
10	50	M	264	150	10+	II+	Moderate*	Moderately advanced	6.1	97	27	1.020	Trace	+	64	Normal	25
11	54	F	180	108	10	II	Advanced	Advanced	4.7	78	39	1.026	Trace	0	64	Normal	15
Average	53		210	120	.....				4.8	86	43	.....			56		20

* Including haziness of the optic disks.

TABLE 3.—*Observations on Patients with Malignant Hypertension*

No.	Age, Years	Sex	Blood Pressure		Duration of Hypertension, Years	Peripheral Arteriosclerosis, Grade	Fundus*		Blood			Urine				Histamine Flare	
			Systolic, Mm. Hg	Diastolic, Mm. Hg			Retinitis	Sclerosis	Erythrocytes, Millions	Hemoglobin, per Cent	Urea, Mg.	Specific Gravity	Albumin	Casts	Urea Clearance, per Cent	Color	Area, Sq. Cm.
1	45	F	280	110	5+	III	Moderate	Advanced	6.2	97	45	1.022	Trace	++	35	Vivid	30
2	52	M	210	140	4	IV	Advanced	Advanced	4.4	84	111	1.014	++	++	16	Normal	12
3	34	M	206	130	3—	I	Moderately advanced	Advanced	4.4	84	39	1.013	Trace	+	89	Pale	18
4	66	M	200	110	Unknown	II+	Slight	Advanced	5.0	91	36	1.020	Trace	+	87	Normal	7
5	51	M	280	110	4	II+	Slight	Moderately advanced	5.1	91	40	1.025	Trace	++	57	Normal	5
6	48	M	300	166	Unknown	II+	Advanced	Advanced	4.3	71	66	1.018	+++	0	48	Pale	12
7	55	F	190	120	Unknown	I	Advanced	Moderate	4.1	75	36	1.010	Trace	0	64	Pale	10
8	44	F	250	170	1½+	II	Hemorrhage†	Hemorrhage†	4.0	70	45	1.018	++	++	19	Pale	19
9	40	F	220	160	3—	I+	Advanced	Moderately advanced	4.8	74	27	1.013	Trace	0	49	Pale	17
10	54	F	190	110	Unknown	I	Slight	Moderate	5.3	91	36	1.020	0	0	98	Normal	12
11	47	F	216	128	5+	I+	Advanced	Moderate	4.4	78	36	1.020	Trace	0	50	Normal	17
12	43	F	260	150	8	III	Moderate	Moderate	4.2	85	39	1.013	0	0	53	Pale	13
13	49	M	180	96	5	I	Moderate	Moderate	4.6	85	45	1.012	0	0	61	Normal	27
14	32	F	214	124	5+	I+	Slight	Moderate	4.9	79	36	1.018	Trace	+	55	Pale	12
15	27	F	240	140	3	I	Advanced	Advanced	4.2	71	30	1.019	Trace	0	55	Normal	17
16	26	F	170	110	4	I	Slight	Slight	4.6	78	39	1.024	0	0	49	Normal	25
Average	45		225	130					4.7	82	44				55		16

* Neuroretinal edema present in all cases.
† Extensive bilateral vitreous hemorrhage.

one half of the average in normal persons. A summary of the observations is presented in table 3.

As a general rule the variations in the area of the flares on the two forearms and in the size of the flares on the same arm at different times were of smaller magnitude in patients with arteriosclerosis or hypertension than in normal persons. This was particularly true in those with flares of low normal or definitely reduced area.

The frequency distribution of the areas of the flares in normal persons and in the patients with arteriosclerosis, benign hypertension and malignant hypertension is presented in charts 1 and 2. The average values for age, blood pressure and area of the flare in all groups of patients are given in table 4.

TABLE 4.—*Table of Average Values*

Condition	Number of Cases	Age, Years	Blood Pressure		Area of Histamine Flare, Sq. Cm.
			Systolic, Mm. Hg	Diastolic, Mm. Hg	
Normal	30	35	118	73	31
Arteriosclerosis, grades I and II	11	65	133	73	22
Arteriosclerosis, grades III and IV	14	68	131	72	18
Benign hypertension	21	51	196	110	29
Hypertension of intermediate grade	11	53	210	120	20
Malignant hypertension	16	45	225	130	16

COMMENT

The results of the present investigation demonstrate that in patients with advanced arteriosclerosis and in those with essential hypertension of the intermediate and malignant types the area of the flare produced by the intradermal injection of histamine usually is diminished. A tendency toward flares of reduced size is observed in patients with normal blood pressure and slight or moderate degrees of arteriosclerosis, although the area is usually within the lower range of normal. Patients with essential hypertension of the benign type have flares of normal area, even though arteriosclerosis also is present.

Under the conditions of the present study diminution in the area of the histamine flare may result from: (1) an interruption of the pathway of the axon reflex through which the stimulus for dilation reaches the strong arterioles of the skin, (2) a reduction in the amount of available blood that can flow into the dilated strong arterioles and through them into the minute vessels of the skin and (3) anatomic or functional changes in the strong arterioles or in the minute vessels which interfere with the normal dilatation of these vessels. There is at present no method available by means of which one may test the functional integrity of the axon reflex alone. It is not probable, however, that a disturbance of the nerve pathways is the primary factor responsible for

the diminished flares in patients with arteriosclerosis or hypertension of the intermediate and malignant types.

The arterioles in patients with senile arteriosclerosis may show slight fatty degeneration in the media, but no other changes are present.[7] It is not probable that such minor alterations are responsible for the diminished histamine flares in these patients. There is also no evidence of an abnormal degree of arteriolar contraction in arteriosclerosis. The most logical explanation of the occurrence of reduced flares in patients with arteriosclerosis and normal blood pressure, therefore, would seem to be that the arteriosclerotic changes in the large and small arteries are accompanied by a reduction in the blood flow of sufficient magnitude to interfere with the full development of the flare.

The observations on the patients with benign hypertension are of considerable significance. The occurrence of flares of normal size in these patients in the presence of various degrees of arteriosclerosis indicates that the factor responsible for the reduced flares in persons with arteriosclerosis and normal blood pressure is not of importance in the presence of hypertension. It follows, therefore, that the diminution in the area of the histamine flare observed in patients with intermediate and malignant hypertension cannot be attributed to the accompanying arteriosclerosis. The degrees of arteriosclerosis were approximately the same in the patients with intermediate or malignant hypertension as in those with benign hypertension. It is not probable that similar changes in the larger vessels exert a different effect in different types or degrees of hypertension.

The characteristic feature of the pathologic process of the intermediate and malignant types of hypertension is widespread hypertrophy of the media and proliferation of the intima of the arterioles.[8] These changes have been observed in practically all the organs and tissues of the body. Relatively few observations have been made, however, on the arterioles of the skin. Fishberg [9] found no changes in the cutaneous arterioles in seventeen cases of essential hypertension, and Watanabe [10] observed thickening of the small arterioles of the skin in only six of one hundred and sixteen cases. Fahr,[11] on the other hand, reported

7. Evans, G.: A Contribution to the Study of Arteriosclerosis, with Special Reference to Its Relation to Chronic Renal Disease, Quart. J. Med. **14**:215, 1921. Keith, Wagener and Kernohan.[1b]

8. Keith, Wagener and Kernohan.[1b] Kernohan, Anderson and Keith.[2]

9. Fishberg, A. M.: Anatomic Findings in Essential Hypertension, Arch. Int. Med. **35**:650 (May) 1925.

10. Watanabe, S.: Ueber die Arteriosklerose der Hautgefässe, Schweiz. med. Wchnschr. **51**:780, 1921.

11. Fahr, T.: Ueber die Beziehungen von Arteriolensklerose, Hypertonie und Herzhypertrophie, Virchows Arch. f. path. Anat. **239**:41, 1922.

that the media of the cutaneous arterioles frequently is well developed in both benign and malignant hypertension, and Kinsella [12] recently made similar observations. Whether alterations of this kind are responsible for the reduction in the area of the histamine flare in patients with intermediate or malignant hypertension cannot be stated. There is considerable evidence to support the view of Volhard [3] that the change from benign to malignant hypertension is due to the occurrence of generalized vasoconstriction. If the arterioles of the skin are involved in this general angiospasm it is conceivable that the increase in tone might be of such intensity that the usual histamine stimulus could no longer cause normal vasodilatation. The area of the flare, therefore, would be diminished. The reduction in the size of the flare in patients with hypertension of intermediate grade might be accounted for in the same way.

Anatomic changes in the minute vessels of the skin (terminal arterioles, capillaries, collecting venules and subpapillary venous plexus) are not present in patients with hypertension. Lewis [4] demonstrated, however, that these vessels are capable of active variations in tone. If the tone of the minute vessels of the skin were increased sufficiently to interfere with the passive filling of these vessels, even though normal arteriolar dilatation did occur in response to histamine, this change could account for the reduced flares in malignant and intermediate hypertension. Further studies are necessary before a final decision can be made as to the relative importance of anatomic changes in the strong arterioles and alterations in the functional state of the arterioles and minute vessels of the skin in limiting the area of the flares.

The color of the flare frequently was abnormally pale in patients with advanced arteriosclerosis and normal blood pressure and in those with hypertension of the malignant type. Although no definite relationship was observed between this change and diminution in the area of the flare, it is probable that they have a common pathogenesis.

The studies of Keith and his associates [8] established the gravity of the prognosis in patients with essential hypertension of the intermediate and malignant types. It is, therefore, of considerable importance that these types of hypertension be recognized accurately, and any procedure that will aid in their identification must be considered of value. Since the area of the histamine flare usually is diminished in patients with malignant hypertension, and with few exceptions is reduced below normal or to the lower limits of normal in the presence of hypertension of the intermediate grade, observations on the area of the flare should prove a useful adjunct in distinguishing these conditions from benign hypertension. Careful ophthalmoscopic examination is, of course, of

12. Kinsella, R. A.: Personal communication to the authors.

more fundamental diagnostic importance, but occasions may be encountered in which the ophthalmoscopic picture is misleading. For instance, the occurrence of papilledema and elevated blood pressure in a patient with an unrecognized tumor of the brain might lead one to suspect malignant hypertension. The presence of a normal histamine flare in such a patient would warn against accepting the diagnosis of malignant hypertension without further consideration. It would seem, therefore, that observations on the area of the flare produced by the intradermal injection of histamine might be included to advantage as a routine part of the clinical study of all patients with essential hypertension.

SUMMARY AND CONCLUSIONS

1. The area of the flare produced by injecting 0.02 cc. of a 1:2,000 solution of histamine dihydrochloride into the skin of the midforearm was measured in five groups: (1) normal persons, (2) patients with arteriosclerosis and normal blood pressure, (3) patients with benign essential hypertension, (4) patients with hypertension of the intermediate grade and (5) patients with malignant hypertension.

2. The average area of the flare in thirty normal persons was 31 sq. cm., and the smallest flare recorded had an area of 18 sq. cm.

3. A distinct tendency toward flares of diminished size was observed in the patients with arteriosclerosis and normal blood pressure. In eleven patients with slight or moderate degrees of arteriosclerosis the average area of the flare was 22 sq. cm., while the average area in fourteen patients with advanced arteriosclerosis was 18 sq. cm. Three patients of the first group and nine of the second had flares of smaller size than the smallest obtained in a normal person.

4. The area of the flare was within the limits of normal in all of twenty-one patients with benign essential hypertension, and the average area for the group was 29 sq. cm.

5. The average area of the flare in eleven patients with hypertension of the intermediate grade was reduced to 20 sq. cm. Four of these patients had smaller flares than the smallest observed in a normal person.

6. In eleven of sixteen patients with malignant hypertension the area of the flare was less than the smallest recorded in a normal person, while in only three did it exceed 24 sq. cm. The average area for the group was 16 sq. cm., approximately one-half the average in normal persons.

7. The results of the investigation indicate that observations on the area of the histamine flare should prove a useful adjunct in distinguishing the intermediate and malignant types of hypertension from the benign form.

TRUE NONPARASITIC CHYLURIA ASSOCIATED WITH MENSTRUATION

REPORT OF A CASE

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This case is recorded because of the rarity of the condition and because it showed a feature which has not to our knowledge been noted in cases hitherto reported, namely, the association of chyluria with menstruation.

REPORT OF CASE

The patient, a married woman, aged 28, of British nationality, first came to our attention in November, 1931, when her husband (a doctor) sought our advice because she was passing milky urine. It soon became apparent that the condition was chyluria. We interviewed the patient and obtained the following history:

Except for the common ailments of childhood she had always enjoyed excellent health. Normal menstruation commenced just before the age of 13; it was always normal. At 16, the patient began to pass milky urine for the first time; this was ascribed to a chill after bathing. For about six months the urine was almost always milky, and then, without special treatment, it became normal again. During this time the patient had occasional momentary attacks of pain and stoppage of micturition.

There was no recurrence of the trouble for nearly twelve years. The patient married in 1928 and gave birth to a child in 1930, labor pursuing a normal course; she noticed nothing unusual about the urine during pregnancy. But early in September, 1931, following a menstrual period, the urine again became milky for two or three days. This occurred after subsequent menstrual periods, at first only after each alternate period. The milky urine appeared as the menstrual flow ceased, and it continued thus for about four days. On one occasion micturition was momentarily impeded by the passage of a clot. She felt no ill effects beyond a premonitory sense of chilliness and general aching immediately before the onset of the attack. Often the urine was clear in the morning, becoming milky toward evening, especially after exercise. She did not lose weight.

Except for a short holiday in the north of France, in 1928, she had never been abroad.

Our colleague, Dr. Paige Arnold, made a roentgen examination and reported the following: Nothing abnormal could be detected in the right or left lung, heart, great vessels or mediastinum. Calcification of some of the cartilages of the ribs was apparent; in view of the age and the sex of the patient, this was an early change. Some of the lower thoracic vertebrae showed marginal processes in

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relation to the anterior surfaces of the vertebral bodies. The right and left renal shadows were of normal size and in the normal position in the peritoneal cavity. An aggregation of shadows could be observed at the level of the fourth lumbar vertebra in the right side of the peritoneal cavity. No evidence of abnormality could be observed in the pelvis.

Urography was performed according to the technic of Abrodil; no abnormality in function could be detected in either the right or the left kidney.

The patient was later examined by Prof. Wilkie and Mr. Wade at their clinic in Edinburgh, when complete cystoscopic and pyelographic examinations were carried out; unfortunately, the chyluria had ceased before the examination.

The wall of the bladder was found to be normal. The ureters were readily catheterized and normal urine was obtained from the pelvis of both kidneys.

Pyelograms made of the kidneys showed no abnormality of outline.

Laboratory Findings.—The first specimen of urine, examined on Nov. 25, 1931, showed the following features: It was creamy white, with a faint tinge of pink. On standing or centrifugation, it still remained homogeneously white and opaque, but a small amount of blood was deposited. No "skin" or clot was formed. No globules of fat were visible. The urine gave a slightly alkaline reaction to litmus. The specific gravity was 1.018.

Microscopic examination of the deposit revealed numerous red blood cells and lymphocytes, all of which appeared fresh and not autolyzed. Threads of fibrin were present; there was no pus, and no organisms were found. Filariae were not found. (Inoculation of the deposit into a guinea-pig gave a negative result; there was no evidence of the presence of tubercle bacilli.) When a specimen of the urine was shaken with ether, considerable clearing of the milky opacity occurred, but a flocculent precipitate was deposited, and the supernatant fluid remained opalescent. Complete extraction with ether yielded 0.56 Gm. of total ether-soluble substances per hundred cubic centimeters.

A second specimen of urine was examined on Jan. 23, 1932. To the naked eye and under the microscope the appearances were identical with those of the first specimen, though the lymphocytes were even more numerous. They were present in much greater numbers than could be accounted for by the presence of normal blood.

On this occasion the uppermost part of the centrifugated urine was examined microscopically, but no globules of fat could be detected. The reaction was alkaline; the specific gravity, 1.018. There was no dextrose.

The white precipitate which was formed on extraction with ether was composed of proteins the molecules of which were apparently loosely linked to the molecules of the fats in a colloidal suspension. The protein linked to the fats was 0.211 per cent of the total. This was composed of the globulin fraction, which was soluble in a 10 per cent solution of sodium chloride and warm water, and the albumin fraction. After these protein fractions were removed, the urine still contained the following proteins: a trace of nucleoprotein and serum albumin, coagulating at 74 C., which together composed 0.75 per cent of the total protein. There was therefore 0.961 per cent of total protein present. The total ether-soluble substances present equaled 0.99 Gm. per hundred cubic centimeters. This included neutral fat, free fatty acids, cholesterol and lecithin. Two-hundredths gram of cholesterol was isolated from 100 cc.

A third specimen of urine was examined on May 4. The blood, protein and fat were present as before; numerous lymphocytes were noted. The content of fat was not estimated.

A fourth specimen was examined on June 14. The characteristics were as before; on this occasion, 1.56 per cent of the total ether-soluble substances was present. There was more blood than in the previous specimens. The patient then volunteered the statement that before the onset of chyluria she felt a sensation of tension in the pelvis, and then "something seemed to give way" and the next urine passed was milky. She was having trouble with clots in the bladder.

A specimen of urine was examined on February 4, during the interval between the second and third examinations. It was clear and normal in appearance. There was a slightly alkaline reaction to litmus. The specific gravity was 1.016. No protein could be detected by any of the tests. There was no dextrose or fat present.

On microscopic examination the deposit showed only a little mucus and a few epithelial cells. No lymphocytes, red blood cells or casts were seen.

Examinations of the blood were made on several occasions, both during the attacks of chyluria and during the intervals between the attacks. Beyond slight secondary anemia, no abnormality was found. There was no eosinophilia, and Filariae were not seen in spite of a long search.

COMMENT

In spite of the rarity of the condition, a fairly large number of cases of nonparasitic chyluria have been recorded; we have been able to collect over a hundred from the literature. On careful scrutiny, however, some of the cases do not present the cardinal features of true chyluria, and it is obvious that there has been a great deal of confusion between the different forms of milky urine. Chyluria may be simulated by various other substances, such as pus, phosphates or artificial additions, which cause milky opacity of the urine. The most elementary chemical and microscopic examinations of the urine will usually suffice to exclude such errors.

That fat is demonstrated in the urine does not necessarily imply that the fat is due to the presence of chyle. The lipuria which sometimes occurs in diabetes mellitus and rarely in fractures and the pseudochyluria of some forms of nephritis must be distinguished from true chyluria. Complete clearing of the opacity when the specimen is shaken with ether and the occurrence of the fat in the form of visible globules usually indicate that the condition is one of lipuria and not of chyluria.

To prove that the milky substance is chyle, it is obviously necessary to show that it possesses most, if not all, of the properties of chyle, i. e., fat-laden lymph. The essential feature of truly chylous urine is the presence of (1) fat, (2) protein and (3) lymphocytes.

Fat.—The fat is usually present in molecular form; that is, the particles are so small that they cannot be seen or separated by centrifugation (Golding-Bird, quoted by Hertz). The molecules of fat are apparently loosely linked with the molecules of protein, because when the fat is dissolved in ether, a precipitate of protein is produced; this

phenomenon has been expressed by most observers as partial clearing after shaking with ether.

Protein.—The protein should be present in the urine, as it is in chyle, in approximately three times the amount of fat. The amount of fat in the chyle is of course variable, depending on the nature of the diet and the state of the digestion. Also, if protein is constantly present in the urine in the intervals between the attacks of chyluria, owing to coincident nephritis, it should be taken into account.

Lymphocytes.—Lymphocytes are present in normal lymph and therefore in chyle. It is curious that previous observers have not specifically noted lymphocytes but have been content to call the cells leukocytes or white corpuscles. Charteris, however, recorded the presence of lymphocytes in his case.

The amount of dextrose in the chyle is only 0.1 per cent, so that the minute quantity which is present in the chylous urine escapes detection by the ordinary copper-reduction tests. Brandenburg described a case of chyluria in a child in whom a fairly high percentage of sugar was present in the urine, but in whom only very transient chyluria existed; this was not proved to be true chyluria.

Blood is normally found in cases of chyluria, presumably coming from the torn superficial blood vessels at the site of the ruptured lymphatic glands. In our case some specimens contained a considerable amount of blood, but the large number of lymphocytes could still be seen.

Having proved that the abnormal constituent in the urine partakes of the character of chyle, one can then separate cases of parasitic origin from the less well defined group of nonparasitic cases, although the mechanism of production is probably similar in both groups. The mere absence of Filariae does not negate a past infection, for the parasites may die out and yet obstruct the lymphatic glands by their dead bodies or by secondary inflammatory fibrosis, with the result that, if the patient has been at any time resident in a district in which filariasis is endemic, the chyluria may be assumed to be filarial unless convincing evidence of another etiologic factor is forthcoming.

In the present case, the possibility of filariasis and allied parasitic infestations seemed to be excluded by the fact that, apart from a short holiday in the north of France, the patient had never been outside the British Isles.

Two theories have been advanced as to the mode of production of chyluria. The first of these, now practically abandoned, is called the secretory theory, which supposes that the fat exists in the blood in excess and is passed by the renal epithelium. This theory, however, cannot explain unilateral cases (Kutzmann and Wood), and chemical exami-

nation of the blood has never demonstrated excess of fat, nor have any casts been noted in the urine.

The alternative theory, which was a consequence of the study of parasitic chyluria, may be termed the mechanical theory. That is to say, chyluria is due to the simple admixture of chyle with urine caused by some abnormal communication between the lymphatic vessels and the urinary tract. Such a fistulous condition is preceded by obstruction somewhere between the lymphatic trunks of the mesentery and the upper end of the thoracic duct; back pressure then takes place, the valves become faulty and the lymphatics dilate. Finally, a retrograde flow of chyle takes place via the lumbar channels to the kidney and to the lymphatic vessels of the bladder; these poorly supported vessels give way, and chylous urine is voided. This theory also explains unilateral cases and the presence of blood, which is probably caused by a rupture of the lymphatic varix. The intermittency so frequently noted in chyluria is more readily explicable by this theory than by any other.

Whereas there appears to be little or no doubt that filarial infection may cause lymphatic stasis of such character that chyluria is produced, various other lesions have also been shown to produce it. Because of the rarity and the relatively benign course of nonparasitic chyluria, only a few autopsies have been performed. In some of these, no cause was found for the chyluria (Osler and Roberts). In others, an obstruction of the thoracic duct was demonstrated, but the lymphatic communication with the urinary tract could not be found. Thus, Oehme found secondary malignant glands pressing on the thoracic duct in a case of carcinoma of the stomach with chyluria; in Port's case tuberculous glands compressed the duct at the level of the left bronchus, and Mackenzie demonstrated great dilatation and thickening of the thoracic duct.

Some observers noted dilated lymphatics in relation to the kidney or the bladder but found no cause for the condition (Ponfick, Havelburg and Coryllos and Portocalis). Hertz was able to demonstrate a constriction of the thoracic duct above the diaphragm and a ruptured lymphatic vessel in the wall of the bladder.

The most notable observations were probably those of Pope and Bloch, who in their cases actually saw chyle entering the urinary tract. Such evidence, though not conclusive, goes a long way toward confirming the second, or mechanical, theory of the mode of production of chyluria. In this connection, it must be remembered that the postmortem demonstration of lesions of the lymphatic vessels is a difficult procedure, and unless some special method of injection is used, it is likely that the abnormality will be overlooked.

On reading through the literature on chyluria one is impressed with the fact that all of the cases have shown marked intermittency, the

recurrences of chyluria being in some cases apparently associated with such factors as posture, exercise, diet and pregnancy and in other cases irregular and not obviously related to an extraneous factor. Various theories, some of them rather fantastic, have been put forward to explain the influence of posture, and most of the writers on the subject have been somewhat puzzled by this feature of intermittency.

If one considers the pathologic nature of chyluria, however, the intermittency seems to be natural, for if the generally accepted view is correct, the condition would seem to be analogous to hematemesis occurring in cases of cirrhosis of the liver but affecting the lymphatics instead of the veins. One does not expect continuous hemorrhage from a dilated esophageal varix; when the congestion of the veins is relieved by the bleeding, coagulation and healing tend to follow. Lymph also contains fibrinogen and can form a clot, though the process may be retarded when the site of the rupture is bathed by urine. The freshly formed clot is liable to be broken down when there occurs in the lymphatics a slight increase of pressure such as may be caused by the weight of the column of lymph above the pelvis in the upright posture, if the valves are incompetent, or when muscular action increases the return of the lymph from the lower limbs via the iliac and the lumbar vessels. In the same way, the ingestion of a fatty meal would possibly be sufficient to cause a fresh discharge of chyle by increasing the flow of lymph in the mesenteric vessels.

It is to be noted, too, that the absence of chyle from the urine does not necessarily indicate that the leakage is sealed off, as the lymph in the mesenteric lymphatic glands contains practically no fat in the absence of active absorption of fat from the intestines; it may continue to escape into the urine, giving rise to lymphuria, as was so ably demonstrated by Hertz. Such lymphous urine appears to be quite clear.

In several of the cases of chyluria reported there were long intervals of freedom from the trouble; in the case described here, there was an interval of twelve years during which no chyluria occurred even with the added strain of pregnancy. It is easier to understand such intermissions if chyluria is regarded as an accident in the development of a collateral circulation of lymph in the abdomen.

Anastomotic channels, hitherto quite small, must be dilated in order to convey the lymph by way of the pelvis and the anterior abdominal wall to the right thoracic duct. The modified system can cope well with the flow of lymph, but there are weak points in its course, just as in the esophageal veins in a case of cirrhosis such weak points are often to be found where the vessels can bulge unsupported into a hollow viscus. It does not follow that chyluria will necessarily occur. There must be a relatively large number of cases of partial or complete obstruction of the thoracic duct by aneurysms, enlarged mediastinal glands and growths

in the thorax, as compared with the small number of cases of chyluria. Nor will the discrepancy be accounted for by the occasional occurrence of chylous effusions in the pleural and peritoneal cavities. The immediate cause of the rupture of the weakened lymphatic on the first occasion is usually not obvious, but any subsequent slight rise of tension in the abdominal and pelvic lymphatics may precipitate a fresh escape of lymph, which ceases as soon as the pressure is relieved. Thus repeated attacks of chyluria may occur, until the point of rupture is finally more firmly occluded by the deposition of successive layers of fibrin, and healing takes place.

It seems impossible to advance a convincing explanation of the occurrence of an attack of chyluria just after menstruation; it seemed to occur too often in our case to be merely fortuitous. The onset did not coincide with the stage of premenstrual congestion.

We realize that the report of this case is incomplete; the observations were brought to a sudden end by the cessation of the chyluria during the rest in bed preparatory to cystoscopic examination, and no recurrence has yet taken place. The patient, of course, has never regarded herself as an invalid, and it did not appear justifiable to inconvenience her by too much experimental investigation, especially as the matter is one of chiefly academic interest.

Prof. D. P. Wilkie and Mr. Wade, of Edinburgh, permitted us to use the report of their cystoscopic and pyelographic observations, and our colleague, Dr. Paige Arnold, his roentgenographic report.

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THE ACID-BASE BALANCE IN PATHOLOGIC CONDITIONS

III. SERUM ELECTROLYTE CHANGES IN ACUTE MERCURIC CHLORIDE POISONING

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It has been recognized for a considerable period of time that aside from a marked increase in the nonprotein nitrogen constituents of the blood, a definite lowering of the blood chloride is characteristic of acute mercuric chloride poisoning. In 1915 Woods [1] observed a lowering of the blood chloride in a case of mercuric chloride poisoning. Similar observations have been made by Lewis and Rivers,[2] Campbell,[3] Killian,[4] Sunderman, Austin and Camack [5] and Trusler, Fisher and Richardson.[6] The last mentioned workers also noted marked hypochloremia in dogs given mercuric chloride. Sunderman, Austin and Camack,[5] in their case of mercuric chloride poisoning, observed in addition to a lowering of chloride a decrease in the serum total base. This has also been the observation of Peters [7] and Bruckman.

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1. Woods, A. C.: Studies of Nitrogen Partition in the Blood and Spinal Fluid with Especial Reference to the Possible Causation of Albuminuric Retinitis, Arch. Int. Med. **16**:577 (Oct.) 1915.

2. Lewis, D. S., and Rivers, T. M.: Chemical Studies on a Case of Bichloride Poisoning, Bull. Johns Hopkins Hosp. **27**:193, 1916.

3. Campbell, W. R.: Observations on Acute Mercuric Chloride Nephrosis with a Report of Two Cases, Arch. Int. Med. **20**:919 (Dec.) 1917.

4. Killian, J. A.: A Note on the Blood Chlorides in Mercuric Chloride Nephrosis, J. Lab. & Clin. Med. **7**:129, 1921.

5. Sunderman, F. W.; Austin, J. H., and Camack, J. G.: Studies of Serum Electrolytes: III. In Infections, Nephritis, and Other Pathological Conditions, J. Clin. Investigation **6**:37, 1928.

6. Trusler, H. M.; Fisher, W. S., and Richardson, C. L.: Chemical Changes in the Blood in Mercuric Chloride Poisoning: Mechanism and Significance of Hypochloremia, Arch. Int. Med. **41**:234 (Feb.) 1928.

7. Peters, J. P., and Van Slyke, D. D.: Quantitative Clinical Chemistry: Interpretations, Baltimore, Williams & Wilkins Company, 1931, vol. 1, p. 1074.

During the last five years it has been possible to make a study of the acid-base balance of the serum in eleven cases of mercuric chloride poisoning. Since the literature contains relatively few data of this type on a series of cases it seemed desirable to present our observations.

The method of collecting specimens of blood and the procedures employed in studying the acid-base balance were essentially those given elsewhere.[8]

REPORT OF CASES

CASE 1.—F. T., a man, aged 66, was admitted to the hospital on Sept. 16, 1928, twenty-four hours after having taken three tablets of corrosive mercuric chloride. He vomited shortly after taking the drug, and the vomitus contained the greater part of two tablets. Treatment consisted of administering sodium thiosulphate daily, alkaline fluids by mouth and colonic irrigations with alkaline fluids. At no time was the patient anuretic, and he vomited only on the first day of hospitalization. He was discharged from the hospital on September 29.

CASE 2.—H. M., a man, aged 24, was admitted to the hospital on Oct. 8, 1928, about half an hour after having taken three tablets of corrosive mercuric chloride. He vomited shortly thereafter, and the vomitus contained blood. Treatment consisted of the daily administration of sodium thiosulphate, alkaline fluids by mouth and intravenous and subcutaneous injections of dextrose and saline solutions. Anuria developed rapidly, and vomiting and diarrhea persisted. The patient became progressively worse and died on October 17.

CASE 3.—H. S., a woman, aged 36, was admitted to the hospital on May 5, 1929, after having taken five tablets of corrosive mercuric chloride five days previously. Nausea, vomiting and bloody diarrhea had been experienced before admission. Anuria was present at the time of admission. Treatment consisted of daily injections of sodium thiosulphate and daily intravenous injections of 1,500 cc. of dextrose and saline solutions. Vomiting and diarrhea persisted until death on May 12.

CASE 4.—S. T., a woman, aged 25, was admitted to the hospital on May 12, 1929, shortly after having taken seven tablets of corrosive mercuric chloride dissolved in hot water. Vomiting occurred a short time thereafter and continued throughout the illness. Anuria developed rapidly and persisted. The treatment consisted of daily injections of sodium thiosulphate and the administration of colonic irrigations and alkaline fluids by mouth. The patient died on May 17.

CASE 5.—P. H., a man, aged 44, was admitted to the hospital on March 7, 1930, an hour and a half after having taken sixteen tablets of corrosive mercuric chloride. Almost immediately thereafter the patient vomited. Milk and white of egg were given. When he was brought to the hospital gastric lavage yielded a large amount of bloody material. Anuria developed rapidly. There were considerable vomiting and diarrhea. The treatment consisted of daily injections of sodium thiosulphate, Fischer's solution (sodium chloride, 1.4 per cent, and sodium carbonate, 2 per cent) administered intravenously and colonic irrigations. The patient became progressively worse and died on March 12.

8. Muntwyler, E.; Way, C. T., and Binns, D.: The Acid-Base Equilibrium in Pathological Conditions: II. Alkalosis Observed in Hypertensive States, J. Clin. Investigation **10**:489, 1931.

CASE 6.—M. C., a woman, aged 35, was admitted to the hospital on April 3, 1930, shortly after having taken six tablets of corrosive mercuric chloride dissolved in water. When brought to the hospital she was given gastric lavage. Vomiting persisted for several days. The patient was never completely anuretic. The treatment consisted of daily injections of sodium thiosulphate, the administration of alkaline fluids by mouth and alkaline colonic irrigations. The patient improved rapidly and was discharged from the hospital on April 19.

CASE 7.—C. B., a woman, aged 26, was admitted to the hospital on April 18, 1933, two days after having taken five tablets of corrosive mercuric chloride. The patient vomited almost immediately and continued to vomit throughout the period of hospitalization. Egg albumin was given. Anuria developed rapidly and remained practically complete until death on April 24. The treatment consisted of gastric lavage, daily injections of sodium thiosulphate, intravenous injections of saline and dextrose solutions and the administration of fluids by mouth.

CASE 8.—E. B., a woman, aged 24, was admitted to the hospital on April 17, 1933, after having taken two tablets of corrosive mercuric chloride. Milk was given shortly thereafter, and vomiting occurred. The vomitus showed fragments of the tablets. The history revealed that the patient had employed two tablets of corrosive mercuric chloride dissolved in a quart (946 cc.) of water for a vaginal douche for a considerable period of time; this practice, however, was discontinued when irritiation, vaginal pain and nocturia were noted, several months before admission. When admitted she was given gastric lavage. The treatment consisted of daily injections of sodium thiosulphate, colonic irrigations and large intravenous and subcutaneous injections of saline solution. The patient was essentially anuretic for six days and then began to excrete small amounts of urine. As urinary excretion increased the nonprotein nitrogen constituents of the blood decreased and the patient rapidly improved. She was discharged from the hospital on May 20. In the early days of hospitalization there were considerable vomiting and diarrhea.

CASE 9.—M. K., a woman, aged 22, was admitted to the hospital on May 26, 1933, shortly after having taken six tablets of corrosive mercuric chloride on an empty stomach. Vomiting occurred almost at once. When brought to the hospital she was given gastric lavage. After the first day of hospitalization anuria developed and continued until death on June 6. The treatment consisted of daily injections of sodium thiosulphate, large subcutaneous and intravenous injections of saline solution and colonic irrigations.

CASE 10.—L. M., a woman, aged 19, was admitted to the hospital on June 3, 1933, thirty minutes after having taken three tablets of corrosive mercuric chloride. Vomiting occurred before admission. When she was admitted to the hospital gastric lavage was given. Severe vomiting persisted, and the patient rapidly became anuretic. The treatment consisted of daily injections of sodium thiosulphate, large intravenous and subcutaneous injections of saline solution and colonic irrigations. The patient rapidly became worse and died on June 7.

CASE 11.—J. T., a man, aged 41, was admitted to the hospital on June 19, 1933, about thirty minutes after having taken five tablets of corrosive mercuric chloride. He vomited several times prior to admission. When he was brought to the hospital gastric lavage was given, and 15 grains (1 Gm.) of sodium thiosulphate was administered intravenously. Milk and saline solution were given by mouth. On June 21, an infusion of saline and dextrose solution (4,000 cc.) was given, and on June 22, an infusion of Ringer's solution (2,000 cc.). The latter was given daily until death on June 25. During the first day of hospitalization 75 cc. of

urine was excreted. From the second day until death the patient was practically anuretic. Severe vomiting was present during the first four days. Bloody diarrhea persisted throughout.

OBSERVATIONS

In the table are given the changes in the acid-base balance of the serum in eleven cases of acute mercuric chloride poisoning. It is readily

Changes in the Serum Acid-Base Balance in Acute Poisoning by Mercuric Chloride

		Serum							Blood			
Case	Date	p_H	Bicarbonate, M.Eq.	Chloride, M.Eq.	Protein, M.Eq.	Total Determined Acid, M.Eq.	Total Base, M.Eq.	Undetermined Acid, M.Eq.	Urea Nitrogen, Mg. per 100 Cc.	Nonprotein Nitrogen, Mg. per 100 Cc.	Creatinine, Mg. per 100 Cc.	Comment
1	9/17/28	....	.....	....	....	.....	.....	....	37	82	2.7	Drug* taken 9/15/28
	9/18/28	7.45	28.84	86.9	....	.....	134.1					
	9/24/28	....	.....	....	....	.....	.....	....	21	40	1.9	Discharged 9/29/28
2	10/ 9/28	....	.....	....	....	.....	.....	....	..	71	4.1	Drug taken 10/8/28
	10/10/28	....	.....	....	....	.....	.....	....	..	..	5.8	
	10/16/28	7.31	14.76	84.8	17.7	117.26	131.5	14.2	..	..	...	Died 10/17/28
3	5/ 7/29	....	.....	....	....	.....	.....	....	113	..	20.0	Drug taken 5/1/29
	5/10/29	7.26	18.36	45.6	....	.....	119.0	....	...	..	....	Died 5/12/29
4	5/15/29	7.27	15.30	82.8	15.3	113.40	133.0	19.6	...	..	....	Drug taken 5/12/29
	5/16/29	7.22	14.40	82.1	....	.....	134.1	....	...	..	....	Died 5/17/29
5	3/10/30	....	.....	....	....	.....	.....	....	102	..	10.0	Drug taken 3/7/30
	3/12/30	7.07	7.03	81.8	15.7	104.53	141.6	37.1	105	..	19.5	Died 3/12/30
6	4/ 8/30	....	.....	....	....	.....	.....	....	...	180	12.0	Drug taken 4/3/30
	4/ 9/30	7.42	17.26	77.5	18.7	113.46	130.8	17.3				
	4/16/30	7.41	19.10	75.5	....	.....	134.8	....	...	...	....	Discharged 4/19/30
7	4/21/33	....	.....	....	....	.....	.....	....	...	113	14.2	Drug taken 4/16/33
	4/24/33	7.34	19.60	66.5	14.9	101.00	149.0	48.0	...	169	12.2	Died 4/24/33
8	4/18/33	....	.....	....	....	.....	.....	....	...	...	4.6	Drug taken 4/17/33
	4/24/33	7.14	12.25	72.2	16.0	100.45	143.0	42.5	...	204	15.3	
	4/28/33	7.24	18.45	80.2	14.1	112.75	150.6	37.8	...	193	15.5	
	5/ 4/33	7.39	28.30	83.1	20.7	132.10	148.1	16.0	...	142	10.6	
	5/13/33	7.48	28.70	98.2	19.8	146.70	148.4	1.7	...	34	3.3	Discharged 5/20/33
	5/24/33	7.38	24.35	103.0	20.3	147.65	147.2	....	...	32	1.6	
9	5/27/33	7.41	23.00	84.6	16.5	124.10	147.5	23.4	...	79	6.6	Drug taken 5/26/33
	6/ 5/33	7.32	14.08	77.6	12.1	103.78	138.7	34.9	57	..	9.4	Died 6/6/33
10	6/ 5/33	7.36	18.46	90.6	16.1	125.16	152.1	26.9	37	..	5.1	Drug taken 6/3/33
	6/ 7/33	7.14	11.26	92.2	12.7	116.16	149.0	32.8	..	108	4.6	Died 6/7/33
11	6/21/33	7.39	19.70	94.6	13.7	128.00	143.3	15.3	39	...	6.2	Drug taken 6/19/33
	6/24/33	7.21	14.60	91.6	13.1	119.30	148.1	28.8	86	...	11.3	Died 6/25/33

* Corrosive mercuric chloride.

apparent that in most instances there was a marked tendency to an uncompensated acidosis accompanied by a lowering of both the serum chloride and the serum total base. The lowest p_H and bicarbonate content were encountered in case 5, in which a p_H of 7.07 and a bicarbonate content of 7.03 milliequivalents were observed. The lowest chloride and total base were observed in case 3, namely, 45.6 and 119 milliequivalents, respectively. With the lowering of the concentration of bicarbonate and chloride the undetermined acid fraction (representing phosphate, sulphate and organic acid) tended to be increased. The

highest value for the undetermined acid (48 milliequivalents) was observed in case 7. The initial specimen from case 8 showed an undetermined acid value of 42.5 milliequivalents. With recovery and coincident elevation of the bicarbonate and chloride concentrations, the undetermined acid decreased to a small value.

COMMENT

The characteristic loss of chloride and total base from the blood in cases of acute mercuric chloride poisoning is undoubtedly due chiefly to a loss resulting from the accompanying vomiting and diarrhea. That vomiting is probably a factor in the loss of chloride was recognized by Lewis and Rivers.[2] They observed that the blood chloride decreased regularly during the period of vomiting and rose after the vomiting had stopped. Trusler, Fisher and Richardson,[6] using dogs, concluded that vomiting was the most important factor. They found that rabbits, which do not vomit, when poisoned with mercuric chloride did not show a marked reduction of the blood chloride. The latter workers also observed a case of mercuric chloride poisoning and found that the decrease in chloride was too great to be accounted for by loss as a result of vomiting. In this case they believed that the loss was brought about by colonic irrigations and gastric lavage, and pointed out that such routine treatment might cause excessive loss of chloride. This danger, they added, can no doubt be mitigated by including physiologic solution of sodium chloride as a component of such solutions.

With loss of fluid from the intestinal tract in cases of mercuric chloride poisoning the patient becomes markedly dehydrated, which results in anuria. The value of forcing fluid in the treatment of mercuric chloride poisoning was brought out experimentally by Haskell, Carder and Coffindaffer [9] in their experiments with dogs. A large percentage of their dogs survived what was considered a fatal dose when given intravenous injections of salt solutions comparatively soon after the oral administration of the poison. Hayman and Priestly [10] emphasized that the maintenance of adequate diuresis during the period of diminished concentration ability forms an essential part of the treatment of mercurial nephrosis. Killian [4] reported the recovery of two patients who, in addition to other treatment, received 0.7 per cent sodium chloride by hypodermoclysis. Consequently, as pointed out by Peters and Van Slyke,[7] it seems that the most important therapeutic measure

9. Haskell, C. C.; Carder, J. R., and Coffindaffer, R. S.: The Value of Forcing Fluid in the Treatment of Mercuric Chloride Poisoning, J. A. M. A. **81**:448 (Aug. 11) 1923.

10. Hayman, J. M., Jr., and Priestly, J. T.: The Importance of Diuresis in the Treatment of Certain Cases of Mercuric Chloride Poisoning, Am. J. M. Sc. **176**:510, 1928.

is an early administration of saline solution intravenously or subcutaneously. This tends to restore to normal the fluid and salt content of the body and to prevent anuria. It is necessary to begin the administration as quickly as possible, for when anuria occurs the recovery of the patient is questionable. Some patients who are not completely anuretic die quickly even though large amounts of saline solution have been administered. In these persons death may undoubtedly be attributed in a large part to shock.[11] That shock was a considerable factor in the rapidly fatal outcome in cases 9 and 10 is unquestionable. These persons were given large intravenous and subcutaneous injections of saline solution immediately, but they remained toxic throughout and soon died.

Of the eleven cases reported recovery occurred in three. Of these three, case 8 is of interest. In this case there was prompt and persistent administration of saline solution. The initial specimen of blood, obtained seven days after the patient had taken the poison, showed a marked uncompensated acidosis and a lowered chloride concentration. Complete anuria was present. During the following month of observation and treatment the bicarbonate and chloride concentrations rose to their normal levels. In this return to normal the bicarbonate concentration rose more rapidly to a maximum than did the chloride and then fell slightly with the further increase in chloride. The constituents of nonprotein nitrogen mounted rapidly during the period of anuria. When, however, excretion of urine was resumed, these constituents quickly returned to normal.

SUMMARY

A study of the acid-base balance of the serum was made in eleven cases of acute mercuric chloride poisoning. The chief disturbances were an uncompensated acidosis, lowering of the chloride and total base and an elevation of the undetermined acid (representing phosphate, sulphate and organic acid).

The therapeutic measures are briefly presented, with emphasis on early intravenous or subcutaneous administration of saline solution to restore to normal the fluid and salt content of the body and to prevent anuria.

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CONGESTIVE HEART FAILURE

XX. CHEYNE-STOKES RESPIRATION AS THE CAUSE OF PAROXYSMAL DYSPNEA AT THE ONSET OF SLEEP

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The starting point of our observations was the fact, noted in a previous study,[1] that patients who complained of seizures of dyspnea at the onset of sleep frequently were observed to have periodic breathing. This was in accord with the statement of Sir James Mackenzie,[2] who wrote:

> Another form of distressed breathing is Cheyne-Stokes respiration. Many elderly people exhibit Cheyne-Stokes respiration without being conscious of it. But in certain forms of heart failure it may occur and becomes so marked that the patient's rest is disturbed during the period of increased breathing. This is preceded by a period when the breathing almost ceases or completely ceases; it may be for a period of half a minute to a minute during which the patient may fall asleep to be awakened up, it may be by a sense of suffocation; on its resumption the breathing is often exaggerated. . . . Occasionally the periods of apnea are so complete and prolonged that the patient wakes up with a sense of great distress, sometimes so severe that he may spring out of bed in his extremity and may then have to breathe heavily and in laboured fashion for many minutes. This is the condition which has received the term "cardiac asthma."

This observation led us to study a group of patients with hypertensive, arteriosclerotic and syphilitic heart disease who had repeated attacks of congestive heart failure over a period of many months. To measure the ventilation was not found feasible as the procedures involved prevented sleep. Consequently it was decided to employ the simple expedient of recording the respirations by means of a pneumograph, a writing pen and a kymograph of the type used with the Benedict-Roth

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1. Harrison, W. G., Jr.; Calhoun, J. A., and Harrison, T. R.: Congestive Heart Failure: XVIII. Clinical Types of Nocturnal Dyspnea, Arch. Int. Med. **53**:561 (April) 1934.

2. Mackenzie, James: Diseases of the Heart, ed. 4, New York, Oxford University Press, 1925, p. 33.

metabolism apparatus. The records of respiration were usually made in the evening between the hours of 8 and 11. As a rule, the patients readily fell asleep when noise was prevented and the lights were turned off, a flash-light being used to watch the tracings on the kymograph. In some instances it was necessary to resort to sedatives, but these were avoided whenever the patient could sleep without them.

In order to clarify the relationship of periodic breathing to dyspnea occurring at the onset of sleep we have attempted to answer the following questions: 1. How frequently do persons who complain of respiratory distress during sleep exhibit Cheyne-Stokes breathing? 2. Why does periodic breathing so frequently occur during sleep? 3. What relation exists between the objective respiratory alterations and the subjective feeling of distress? 3. What is the rôle of the blood gases in producing these objective and subjective phenomena? It may be stated at this point that our observations have shown that two factors are of especial importance in relation to periodic breathing and dyspnea appearing at the onset of sleep. These are (*a*) overventilation and (*b*) depression of the respiratory center occurring suddenly when the subject passes from the waking to the sleeping state. We shall now consider the results of observations in detail.

OBSERVATIONS

1. *Frequency of Cheyne-Stokes Respiration in Patients Complaining of Paroxysmal Dyspnea Occurring at the Onset of Sleep.*—If Mackenzie's theory of the mechanism of paroxysmal dyspnea is correct, one should be able to demonstrate that every patient with this syndrome also has Cheyne-Stokes respiration. For several months we observed hospitalized patients with paroxysmal dyspnea in order to determine whether or not this is the case. It was soon found that many patients of this type do not have Cheyne-Stokes respiration. The patients without periodic breathing usually had their paroxysms of dyspnea after sleeping for one or more hours; none of them had attacks coming on at the onset of sleep. On the other hand, every patient who complained of dyspnea as sleep came on had periodic breathing. During the day the breathing may be regular, but rhythmic variations develop as the patient goes to sleep. In one instance we were unable to observe periodic breathing by inspection, but respiratory curves showed that it was present. Probably there are exceptional cases, but up to the present time we have found none, and it seems safe to state that, as a general rule, patients with attacks of dyspnea coming at the onset of sleep exhibit Cheyne-Stokes respiration. Furthermore, as clinical improvement sets in the cycles gradually diminish in intensity, and simultaneously the paroxysms of dyspnea become less frequent and less severe. Finally

they disappear, but the breathing remains periodic for a longer time and then becomes regular. The important point is that the attacks subside entirely before the periodicity disappears completely. In chart 1 are shown respiratory curves of two patients, both of whom had severe paroxysmal dyspnea coming at the onset of sleep at the time the first (upper) tracings were made and milder dyspnea during the day with each hyperpneic phase of the cyclic breathing. The second records (*B*) were taken in both cases after there had been marked clinical improvement and when the patients were still having occasional mild respiratory distress on going to sleep but none during the day. The later curves

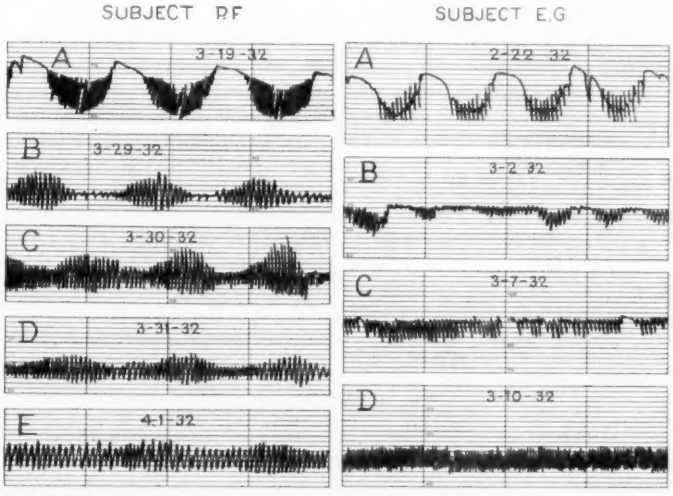

Chart 1.—The curve passes from right to left. The distance between two adjacent vertical lines represents one minute. The successive curves illustrate the progressive gradual disappearance in both patients of Cheyne-Stokes respiration as clinical improvement occurred. When the first tracings (*A*) were taken both patients had severe paroxysmal dyspnea, diurnal as well as nocturnal. At the time of the second tracings (*B*) they had mild attacks on going to sleep but none during the day. When the later records were made both patients were free from subjective respiratory distress.

(*C, D, E*) were all taken after the patients were free from dyspneic seizures. It can be seen that periodic breathing persisted in a mild form for a few days after the cessation of paroxysms, but finally the breathing became regular.

2. *Effect of Sleep on the Respiratory Curve.*—To determine whether the breathing of patients of the type under discussion underwent further alteration during the transition from the waking to the sleeping state,

the time at which subjective respiratory distress is most marked, tracings were made in the evening before, during and after the onset of sleep.

In all instances an attempt was made to estimate the exact status as regards sleep. As used throughout this paper and on the curves the term "awake" implies full consciousness; "dozing" means a somnolent state in which the patients when roused answered spoken questions but did not respond to whispers; "light sleep" signifies that the patient was definitely asleep and could be roused only with some difficulty. The unqualified term "sleep" is used to designate the instances in which the patient was definitely not awake but in which we were unable to decide just how deeply asleep he was.

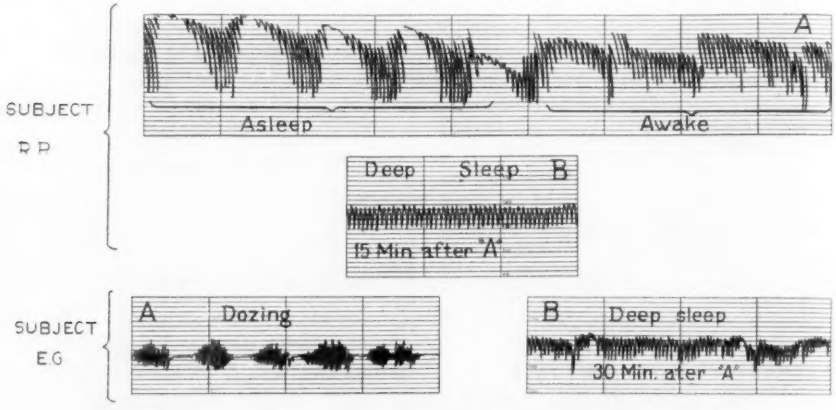

Chart 2.—The curves pass from right to left. The distance between two adjacent vertical lines represents one minute. During the somnolent state both subjects showed well marked Cheyne-Stokes respiration which tended to disappear in deep sleep.

In a number of instances the patients went to sleep rather abruptly, and we could be certain to within a few seconds as to the exact time of the onset of sleep. Examples are shown in chart 2 (subject R. P., curve *A*) and in chart 3 (subject E. G., curves *A, B, C* and *D*). While awake some of the subjects had periodic breathing and some did not. At the moment sleep began, the breathing became less pronounced. Sometimes there was total apnea, and sometimes only a marked decrease in the depth of breathing. Following this initial apnea (relative or absolute) there occurred a period of hyperpnea. (Throughout this paper the term "dyspnea" is used to mean subjective respiratory discomfort, while "hyperpnea" designates the phase of heightened respiratory activity.) This hyperpnea usually lasted about one-half minute and was

followed by a second phase of depression, often more marked than the first, which in turn was likely to be followed by a second hyperpneic phase, and so on, the result being Cheyne-Stokes respiration. In many cases this set in at the moment of sleep; in others it was already present but increased in severity.

In other instances (chart 3, subject J. W. C.) the transition from the waking to the sleeping state was much more gradual. Then the respiration gradually became periodic as the patient dozed. During light sleep the cycle would become more pronounced and there would be occasional short periods of apnea, followed by hyperpnea. During the latter phases the ventilation usually seemed to be greater than during

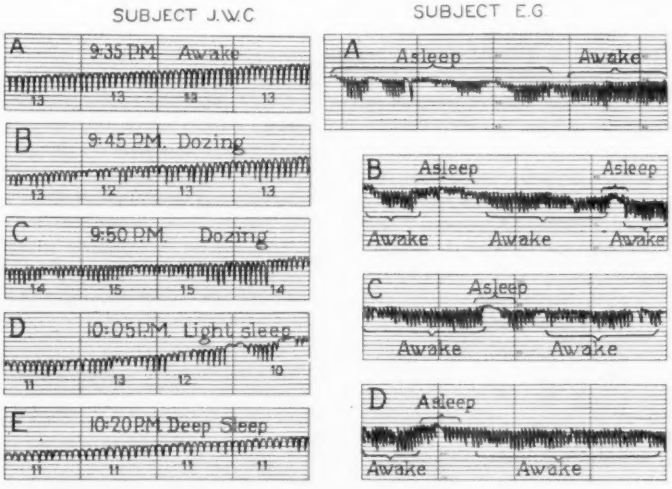

Chart 3.—The curves pass from right to left. The distance between two adjacent vertical lines represents one minute. At the onset of sleep respiratory depression developed, and this was followed by periodic breathing (E.G.). Awakening was associated with greater breathing. The changes in the other subject (J.W.G.) were more gradual but similar. While he was awake the respiration was regular. When he became sleepy and began to doze, periodic breathing developed and after a time there was actual apnea. With the onset of deep sleep the respiration again became regular.

the previous waking period when the breathing was regular. This was judged from the curves, which, being pneumographic and not spirometric tracings, gave accurate information as regards the respiratory rate but may have been misleading in respect to tidal air.

In still other instances there was rapid alternation in the level of consciousness, the subject dozing during hyperpnea and sinking into definite sleep at the onset of apnea. This phenomenon is well recognized

as frequently occurring in patients with Cheyne-Stokes respiration in various diseases. An example of this type of record is seen in chart 2 (subject E. G., curve *A*).

One important feature which was almost invariably observed was the tendency of periodic breathing to disappear entirely or to become much less marked as the subject sank into deep sleep (charts 2 and 3). The only exceptions to this general rule occurred in some of the instances in which morphine had to be administered in large doses in order to induce sleep. Even under such conditions the periodic breathing usually became less pronounced or disappeared as deep sleep developed, but in some cases the reverse effect occurred, the periodicity becoming progressively more pronounced as sleep became more profound. This exceptional result seems to have been related to the action of the drug and does not invalidate the general rule that Cheyne-Stokes breathing becomes more pronounced at the onset of sleep and then tends to disappear, provided, of course, that the subject remains asleep.

Somewhat similar results have been found in normal subjects by Reed and Kleitmann.[3] They noted that the respiration often became irregular during somnolence, and in some instances definite Cheyne-Stokes breathing occurred. As the subjects sank into sound sleep the respiration again became regular.

3. *Subjective Distress in Breathing in Relation to the Respiratory Curve.*—When tracings were being taken on persons who were subject to attacks of paroxysmal dyspnea the patient was instructed to tell us whenever he felt short of breath. In chart 4 are shown examples of the respiratory curves obtained at such times. In the upper left record (*A*) four cycles of Cheyne-Stokes breathing are shown, and it can be seen that the hyperpneic phase was more marked in two of these cycles than in the other two. The onset of dyspnea coincided with the development of marked hyperpnea, as would be expected. In many instances these phases of unusually severe hyperpnea occurred following several cycles during which the apnea became progressively longer as the patient sank into sleep. Then following a long period of apnea the subject would awake as breathing set in. On awakening, the hyperpneic phase would be considerably more marked than in the previous cycles when the patient was asleep or dozing, and coincidentally dyspnea would be severe until the next apneic phase occurred. This sequence of events is illustrated in curves *B* and *D* of chart 4.

In some instances the awakening was immediately preceded by coughing, and the cough seemed to be the "trigger" which caused the patient to awake (chart 4, curve *C*). More commonly cough occurred after the patient had awakened and either during the crescendo part

3. Reed, C. I., and Kleitmann, N.: Am. J. Physiol. **75**:600, 1926.

of hyperpnea or at its height. Whenever the patient awakened, the hyperpneic phase became temporarily more pronounced than during the preceding cycles when the patient had been asleep. This phenomenon is of fundamental importance to a proper understanding of the mechanism of the dyspnea and will be discussed later.

Frequently records of the type illustrated by curve *E* in chart 4 were obtained. In these cases the patient slept during each apneic phase and usually awoke with dyspnea during the crescendo portion of the

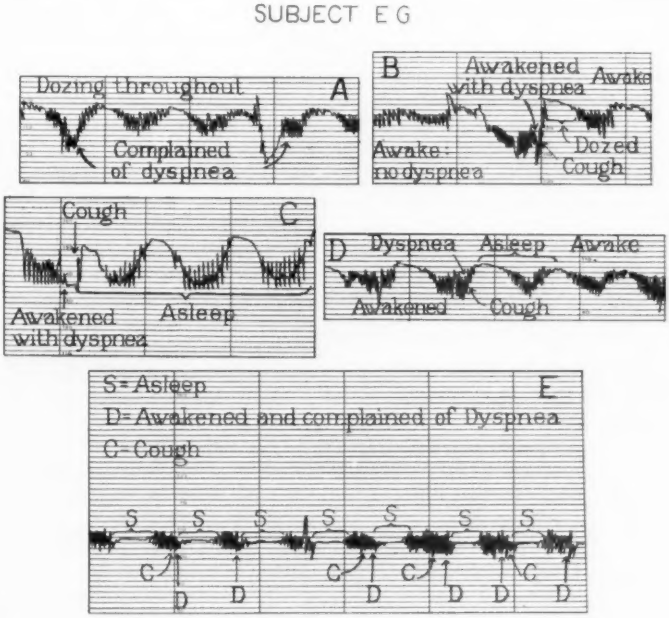

Chart 4.—The curves pass from right to left. The distance between two adjacent vertical lines represents one minute. During the apneic periods the patients tended to doze. Awakening and subjective distress occurred during the crescendo portion of the hyperpneic phase and was associated with an increase in the degree of hyperpnea as compared with the same phase when asleep (*A*, *B* and *C*). On the patient's sinking into sleep there was a tendency for each apneic cycle to become longer until he awakened with subjective dyspnea at the end of an unusually long period of apnea (*D*). Coughing sometimes occurred just before the awakening and at the onset of hyperpnea (*C*); in other instances the cough came after awakening and at the height of hyperpnea (*E*). In the lower curve (*E*) the patient slept during each apneic phase and awakened each time hyperpnea set in.

hyperpneic phase. Occasionally he would remain asleep during hyperpnea, and the record usually showed that this particular cycle was characterized by less violent hyperpnea than the other ones in which he awakened.

With patients who have extremely severe dyspnea one may sometimes obtain curves similar to *D* in chart 4 throughout the whole twenty-four hour period. Such patients are exhausted and fall asleep toward the end of each hyperpneic period. The sleep lasts for from a few seconds to a minute, and then shortly after the resumption of breathing the subject wakes; the breathing becomes still more labored for perhaps a minute or less, and the cycle then repeats itself. Such patients may live for days and never sleep more than a few minutes or seconds at

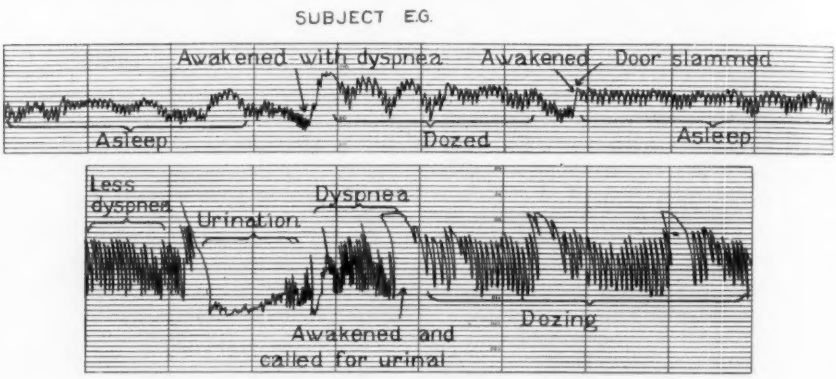

Chart 5.—The curves pass from right to left. The distance between two adjacent vertical lines represents one minute. At the beginning of curve *A* the subject was asleep. When a door slammed he did not immediately awaken but did show an increase in breathing which was followed by several cycles of respiratory periodicity. At length apnea developed, and following this he suddenly awakened with marked hyperpnea and subjective distress. In curve *B* is illustrated the awakening caused by the desire to urinate and associated with hyperpnea and dyspnea. During urination there was respiratory inhibition and then, the patient being awake, the breathing remained greater than when he had been sleeping but not as marked as just before urination.

a time unless they receive sedatives. With improvement in their clinical state the cycles become less marked. With the onset of sleep the apneic phases become progressively longer and the hyperpneic periods more marked until the patient awakes with a dyspneic paroxysm which is simply an unusually severe hyperpneic phase. If, however, this barrier is once passed and sound sleep comes on, the breathing becomes relatively regular and remains so as long as the deep sleep persists.

4. *Effect of Various Stimuli on the Respiratory Curve.*—Any factor which either causes the patient to awaken or decreases the depth of sleep tends to precipitate Cheyne-Stokes respiration and thereby to cause attacks of paroxysmal dyspnea. Cough is probably the most frequent and important of such factors (chart 4) but a number of others have been noted, and examples are shown in charts 5 and 6. The slamming of a door in an adjacent corridor (chart 5, curve *A*) caused the respiration, which had been only slightly irregular, to increase and then become periodic. After several cycles of rhythmic breathing, apnea occurred.

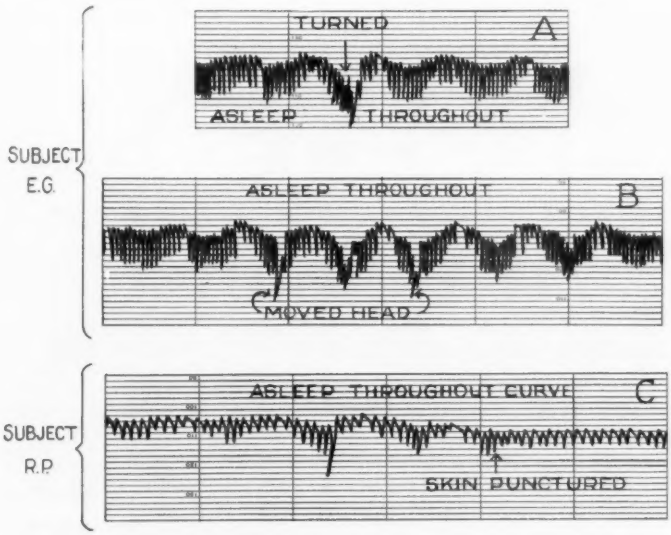

Chart 6.—The curves pass from right to left. The distance between two adjacent vertical lines represents one minute. Movements of the body were associated with respiratory augmentation and a corresponding increase in the degree of periodicity. A more striking effect was obtained by puncturing the skin. Although the patient remained asleep the stimulus was followed by periodic breathing which was progressive for several cycles and then gradually disappeared. It seems evident that the increased breathing produced by the stimulus was responsible for the subsequent periodicity.

With the onset of the next hyperpneic phase the subject awakened and complained of dyspnea, and at this time there was marked augmentation of the breathing. This was followed by a phase of depression, and the subject then gradually returned to sleep.

A similar cycle of events was observed in the same patient on several other occasions, the precipitating factor in these instances being the desire for urination. An example is shown in curve *B* of chart 5.

While half asleep the patient suddenly awoke and called for the urinal. Until this was brought to him he remained extremely dyspneic. As soon as he began to urinate his dyspnea disappeared, and a phase of diminished breathing set in. As stated, this series of events was observed on several occasions, and the patient volunteered the information that many of his dyspneic seizures were precipitated by the desire for urination.

The effect of such "trigger" factors is most marked when they cause the patient to awaken, but definite changes in the respiratory curve can be observed as a result of stimuli which are not sufficiently strong to cause awakening. Examples are shown in chart 6. Turning the body (*A*) or moving the head (*B*) caused well marked increase in the degree of the periodicity of the breathing, which had previously been only slightly irregular. The effect of sticking the skin with a needle (*C*) was even more pronounced; periodic breathing developed, becoming progressively more marked for three cycles and then gradually disappearing.

As a result of the tracings exemplified by charts 4, 5 and 6 one may summarize the relation of stimuli to paroxysmal dyspnea of the type under consideration as follows: Many types of bodily stimuli tend to cause an immediate increase in respiration which is likely to be followed by periodic breathing even though the patient remains asleep. If the stimulus is strong enough to awaken the patient, the hyperpnea is more marked and is likely to be associated with subjective dyspnea. Following this severe hyperpnea periodic breathing usually becomes exaggerated for a few cycles, and there may be subjective distress with each hyperpneic phase of these cycles.

5. *Production of Periodic Breathing by Overventilation.*—The observations which have just been cited suggest that the immediate cause of onset of Cheyne-Stokes respiration occurring in response to a stimulus is overventilation. That this assumption is probably correct is indicated by chart 7 in which it is shown that periodic breathing could be produced by voluntary hyperpnea both in normal subjects and in a patient with cardiac disease. This observation is in no sense original since it was shown by Douglas and Haldane [4] in 1909 that forced breathing in man could cause periodic breathing, and their observation was confirmed by King,[5] who produced typical Cheyne-Stokes respiration in dogs by the same means.

It is planned to publish at a later date the results of a clinical and experimental study of the mechanism of Cheyne-Stokes respiration in general, and at that time the results of our observations in regard to

4. Douglas, G. C., and Haldane, J. B.: J. Physiol. **38**:401, 1909.
5. King, C. E.: Unpublished observations.

the blood gases of patients with cardiac and other diseases will be presented in detail. At present we prefer to draw no conclusions concerning the mechanism of Cheyne-Stokes respiration in general, but it may be stated that in regard to the periodic breathing occurring in patients with cardiac failure there appear to be at least two important physiologic factors, which are:

(*a*) Overventilation Due to Reflex Stimulation of Breathing: In other studies of the present series it has been shown that congestion of the lungs [6] and a rise in venous pressure [7] produce reflex increase in

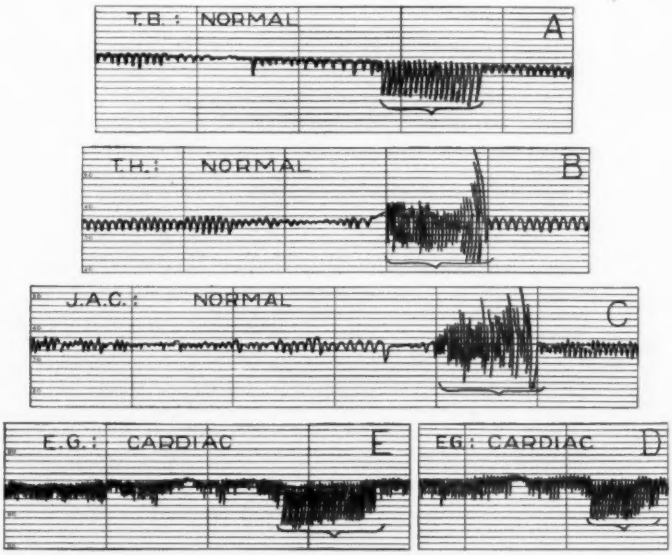

Chart 7.—The curves pass from right to left. The distance between two adjacent vertical lines represents one minute. Voluntary overventilation was followed by respiratory depression in all subjects, and during the recovery from this the breathing was periodic.

breathing. This leads to excretion of carbon dioxide and eventually, when the respiratory depression due to the loss of the gas becomes sufficiently marked to overbalance the reflex stimulation of breathing, apnea results. At the end of apnea there is both chemical and reflex stimulation of breathing, and another cycle results. That this sequence

6. Harrison, T. R.; Calhoun, J. A.; Cullen, G. E.; Wilkins, W. E., and Pilcher, C.: J. Clin. Investigation **11**:133, 1932; Harrison, T. R.; Harrison, W. G., and Marsh, J. A.: Am. J. Physiol., to be published.

7. Harrison, T. R.; Harrison, W. G., and Marsh, J. A.: Am. J. Physiol. **100**:417, 1932.

of events plays a rôle in the production of Cheyne-Stokes respiration is indicated by the fact that the majority of patients with cardiac failure and Cheyne-Stokes respiration do have abnormally low values for arterial carbon dioxide tension. However, overventilation cannot be regarded as the sole factor because some patients with cardiac failure and Cheyne-Stokes respiration have had normal values for arterial carbon dioxide

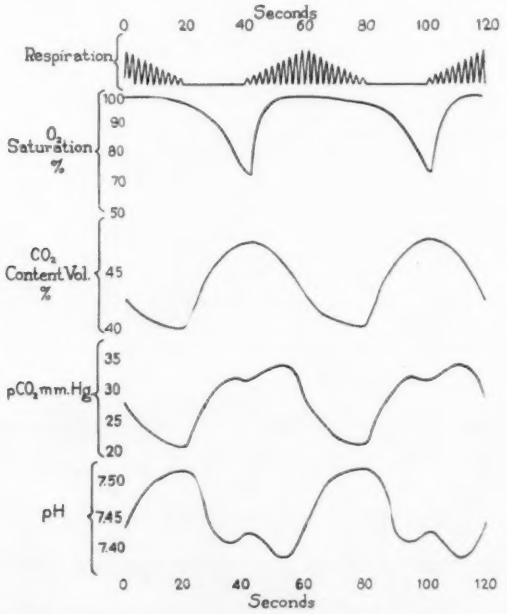

Chart 8.—The curves pass from left to right. This is a diagram and is not based on actual data but is constructed as a result of the general principles arrived at in an as yet incomplete study of the mechanism of experimental Cheyne-Stokes respiration. During apnea the carbon dioxide accumulates rapidly at first and then more slowly, while oxygen behaves in the reverse manner. During the first part of apnea the blood becomes more acid because of carbon dioxide accumulation, but toward the end of apnea there is a rapid conversion of HbO_2 into Hb and as a consequence the p_H tends to become more alkaline. At the onset of breathing the initial change is in carbon dioxide because of its greater diffusion velocity, but after one or two breaths there is a sudden increase in the oxygen saturation with a resulting increase in acidity of the blood. While this is taking place the breathing is crescendo. After the blood has become normally saturated with oxygen the carbon dioxide effect again predominates and further breathing causes the blood to become more alkaline. This causes the respiration to assume the diminuendo character. It is evident that the double peaks in the curves of p_H and pCO_2, which are due to the differences in the physical and physiologic characteristics of oxygen and carbon dioxide, may be important factors in the production of the characteristic periodic breathing.

tension, and furthermore, the periodic breathing is most marked at the onset of sleep, at a time when there is no primary further increase in the ventilation.

(*b*) Depressed Sensitivity of the Respiratory Center: The tendency of morphine and of other respiratory depressants to produce Cheyne-Stokes respiration is well recognized. Sleep is characterized by a general depression in the irritability of the nervous system, and it seems likely that the appearance of periodic breathing at the onset of sleep, both in normal persons and in patients with cardiac disease, is related to depressed sensitivity of the respiratory center. When our patients

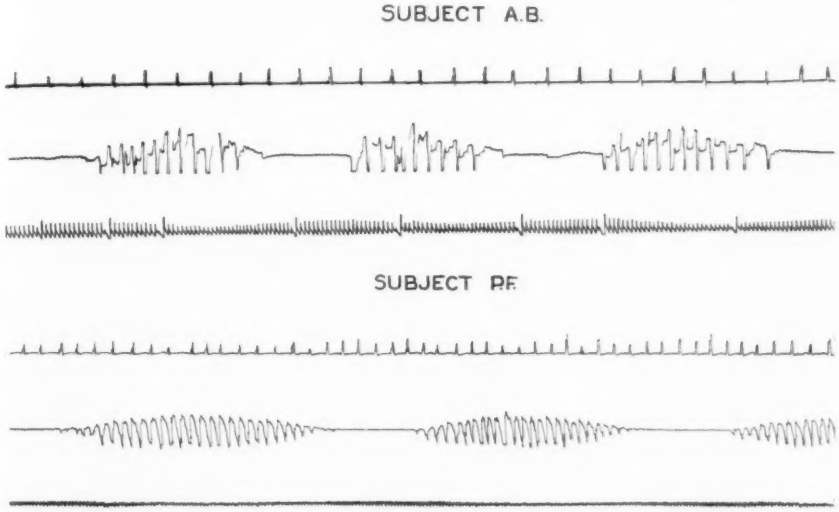

Chart 9.—The curves pass from left to right. In each tracing the upper curve represents time, the intervals being five seconds in the case of A.B., and three seconds in that of P.F. The middle curves designate respiration, and the lower curves indicate blood pressure, which was recorded by means of an Erlanger capsule attached to a blood pressure cuff placed on the subject's arm and inflated to about 100 mm. of mercury. Changes in the amplitude of the excursions reflect alterations in blood pressure. Since the blood pressure rises progressively during apnea (asphyxia) and falls during hyperpnea (relief of asphyxia), it seems that these alterations are results rather than causes of the changes in breathing.

passed suddenly into the sleeping state the breathing was immediately diminished, and usually there was total apnea.

It appears therefore that either of the two factors which have been mentioned may, acting alone, produce periodic respiration, but that in many patients both are operative, the overventilation being continuously present and the additional effect of respiratory depression at the onset

of sleep causing the phenomenon to become more pronounced. However, even though such an explanation would account for the occurrence of periodic alterations of hyperpnea and apnea, it fails to indicate the cause of the peculiar character of the hyperpneic phase, i. e., the progressive increase followed by the steady decrease in the amplitude of the respiratory movements.

6. *Observations Concerning the Cause of the Crescendo and Diminuendo Portions of the Hyperpneic Phase.*—One might suppose that the final result of reflex stimulation plus diminished sensitivity would be such as to produce something approaching normal breathing. Actually this is not usually the case for reasons which are illustrated in chart 8. This diagram does not represent actual data but is based on the general principles arrived at from data obtained by King and Harrison in a study of the mechanism of experimental Cheyne-Stokes breathing.[8]

It can be seen that during apnea the oxygen saturation diminishes slowly at first and more rapidly when the alveolar oxygen tension has decreased to a point corresponding to the steep part of the curve for oxygen dissociation. This decline continues until just after the beginning of breathing, and then the oxygen saturation abruptly rises to a normal or a supernormal level, where it remains throughout the remainder of the hyperpneic phase.

The behavior of carbon dioxide is different. As apnea begins, this gas accumulates in the blood at first rapidly and then more slowly. With the onset of breathing the carbon dioxide content begins to decrease. Because of the lesser diffusion velocity of oxygen this change sets in before the latter gas starts to increase. During the crescendo phase of hyperpnea the rate for loss of carbon dioxide increases, and then the excretion becomes slower as the breathing passes into the diminuendo phase.

These differences between the behavior of the two gases are in accord with what one would expect from the differences in their physical and physiologic properties, the changes in carbon dioxide beginning a little sooner because of its greater diffusion velocity but being gradual because its dissociation curve approaches a straight line. Oxygen, on the other hand, exhibits little change so long as the oxygen tension is in the normal region because at this point its dissociation curve is almost flat. However, when the oxygen pressure is low its dissociation curve is more nearly vertical and hence, once this point has been reached, the decrease (at the end of apnea) and the increase (shortly after the onset of breathing) in the amount of oxygen in the blood occur with great abruptness.

8. This study is not yet complete and will be published later.

The curve for p_H in chart 8 is of special interest. At the beginning of apnea the blood becomes rapidly more acid, but toward the end of apnea there is either no further change or a slight shift toward alkalinity. The latter phenomenon is to be attributed to the simultaneous rapid conversion of oxyhemoglobin into the less acid reduced hemoglobin. At the onset of breathing there is a slight initial rise in p_H because the carbon dioxide begins to decrease immediately. However, this is followed by a second acid peak, which occurs at the same time as, and is due to, the sudden oxygenation of the hemoglobin. Consequently, since the most acid point in the cycle occurs several seconds after the onset of breathing the respiration is crescendo. After the blood has become oxygenated, the further effect of breathing is to cause the blood

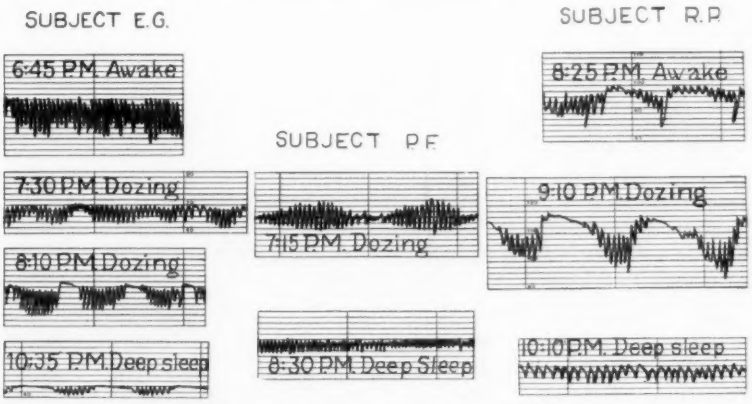

Chart 10.—The curves pass from right to left. The distance between two adjacent vertical lines represents one minute. The curves illustrate the type of breathing at the time when the samples of blood were drawn (table 1).

to become more alkaline from loss of carbon dioxide, and the result is the second or diminuendo portion of the hyperpneic phase. Then apnea occurs and the cycle repeats itself.

The curve for carbon dioxide tension is, as would be expected, similar to the reciprocal of the curve for p_H, the point of highest carbon dioxide tension coming not at the end of apnea but at the time of the secondary rise which occurs during the first part of hyperpnea.

The effect of the irregular behavior of the carbon dioxide tension and the p_H is to produce an "overshooting" both of hyperpnea and of apnea, and this result is of fundamental importance in the production of pronounced Cheyne-Stokes respiration. It does not seem likely that the mechanism under discussion is the sole or even the chief cause of

periodic breathing in general, but it is obvious that such "overshooting" will tend to exaggerate any preexisting tendency toward periodic breathing.

Changes in blood pressure might seem to be another possible cause of the peculiar character of the respiratory movements during the hyperpneic phase, and a number of authors have maintained that this is the case. In order to test this hypothesis we have made simultaneous tracings for blood pressure and respiratory curve, examples of which are shown in chart 9. It can be seen that the blood pressure falls during hyperpnea and rises during apnea. This indicates that the changes in blood pressure are, in the main, the result of alternate development and relief of asphyxia. Hence, it may be concluded that in the type of Cheyne-Stokes respiration under discussion, i. e., that due to congestive heart failure, the alterations in blood pressure are the result and not the cause of the change in breathing.

7. Relation Between Changes in Blood Gases and the Occurrence of Periodic Breathing at the Onset of Sleep.—Analyses of the arterial blood of three patients have been made before and after the onset of sleep. The blood was drawn at a uniform rate throughout a complete respiratory cycle, and consequently the values obtained indicate the average condition of the blood, but they do not represent the actual composition either during apnea or during hyperpnea.

In two instances the patients slept spontaneously; three times morphine was administered in order to secure sleep, but the results did not, except in one observation, differ from those obtained when no sedative was given.

The analyses were made according to the methods used in the other studies in the present series: Oxygen and carbon dioxide were measured according to the Van Slyke-Neill technic, the p_H was determined by Cullen's colorimetric method, and calculations of carbon dioxide tension were made from the Hasselbach equation, a value of 6.1 being assumed for pK^1.

The values for the blood gases are shown in the table and the corresponding respiratory curves may be seen in chart 10. In three observations the patient was awake when the first sample was drawn. As somnolence set in, Cheyne-Stokes respiration developed in the patients who did not already have it (E. G., 12-19 and 3-2) and in the other subject (R. P.), who exhibited slight irregularity when awake, the phenomenon became more marked. Nevertheless, the two samples of blood were in each instance practically identical in composition, no alteration beyond the error of the methods used being observed in oxygen saturation, carbon dioxide pressure or p_H. Consequently, it seems justifiable to conclude that the appearance or increase in the degree of periodic breathing at the onset of sleep is not due to changes in the

composition of the blood but must be ascribed to some other factor. For reasons which have been mentioned we believe that this factor is the rather sudden decrease in sensitivity of the nervous system—and hence of the respiratory center—which occurs at the onset of sleep.

In three instances blood was obtained in the dozing state when Cheyne-Stokes respiration was present, and later during the deep sleep after the breathing had become regular. Constant differences between the oxygen and the carbon dioxide contents of the two samples were not found. In each instance, however, the p_H was measurably lower and the carbon dioxide tension definitely higher in the sample drawn during deep

Alterations in Arterial Blood Gases Associated with Sleep in Patients with Cheyne-Stokes Respiration and Cardiac Failure

Subject	Date	Time	Cheyne-Stokes Respiration	Oxygen Saturation, per Cent	Carbon Dioxide Content, Volumes per Cent	Carbon Dioxide Pressure, Mm. of Mercury	p_H	Comment
E. G.	12/19	5:00	Absent	92.9	53.8	38.3	7.40	Awake
		5:35	Mild	91.0	53.9	39.1	7.39	Dozing; morphine at 5:05 p. m.
	2/28	7:30	Mild	78.8	60.2	45.1	7.38	Dozing
		9:30	Absent	80.1	61.5	49.0	7.35	Deep sleep; no drugs
	3/ 2	6:45	Absent	95.3	62.4	43.4	7.41	Awake (chart 10)
		7:30	Mild	94.8	60.6	43.0	7.40	Dozing, after morphine 0.010 Gm.
		8:10	Moderate	95.3	60.8	43.1	7.40	Dozing
		10:35	Very marked	68.7	68.2	43.4	7.45	Deep sleep, after morphine 0.010 Gm. additional
R. P.	2/27	8:25	Mild	95.7	49.1	34.9	7.40	Awake (chart 10)
		9:10	Marked	95.2	51.1	36.2	7.40	Dozing, after morphine, 0.015 Gm. and caffeine, 0.2 Gm.
		10:10	Absent	90.3	51.4	38.1	7.38	Deep sleep
P. F.	3/29	7:15	Moderate	92.0	51.7	36.0	7.41	Dozing (chart 10)
		8:30	Absent	94.8	52.0	38.6	7.38	Deep sleep* (no drugs)

* This patient awakened while the sample of blood was being obtained; the other subjects remained asleep throughout.

sleep when the breathing was regular than in the previous sample drawn in the somnolent state when Cheyne-Stokes respiration was present.

In one patient who had to be given morphine twice in order to produce deep sleep the periodicity was progressively more marked as sleep became deeper. He exhibited no significant change in his blood in passing from the waking to the somnolent state, although the breathing became periodic. After the second dose of morphine he sank into a deep sleep; Cheyne-Stokes respiration was much more pronounced, and the blood gases exhibited striking changes, the oxygen decreasing, the carbon dioxide content increasing and the p_H rising, but the carbon dioxide tension remaining unchanged.

These observations indicate that the disappearance of Cheyne-Stokes breathing during deep sleep—unlike its appearance during light sleep—

is associated with slight but detectable chemical changes in the arterial blood in the direction of increased acidity and higher carbon dioxide tension. These chemical alterations have been described by others [9] and appear to be a characteristic feature of normal sleep. It seems possible that since overventilation can produce Cheyne-Stokes respiration the disappearance of the periodicity during deep sleep is due to decreased ventilation of the blood with consequent increase in acidity and carbon dioxide tension.

On the other hand, during deep sleep, the periodic breathing may instead of disappearing become exaggerated, and in such an instance, as increasing respiratory depression occurs, apnea becomes longer, and marked oxygen unsaturation develops. The anoxemia results in "overshooting" of the respiration during the next hyperpneic phase because of the mechanism which has been described (increase in acidity at the onset of breathing due to sudden oxygenation of hemoglobin), and this in turn, by making the blood more alkaline, tends to keep the carbon dioxide tension from rising as it normally does during sleep. Hence, the paradoxical condition of the blood—which is overventilated as regards carbon dioxide and insufficiently aerated in respect to oxygen—persists, and this in combination with the depressed sensitivity of the respiratory center causes the periodic breathing to assume and maintain its exaggerated form.

COMMENT

As a result of the data herein reported we are now in a position to return to our original problem, i. e., the cause of the dyspnea appearing at the onset of sleep.

A patient without cardiac disease may have striking Cheyne-Stokes respiration and yet suffer no subjective respiratory distress, provided he has a normal vital capacity. It has been pointed out elsewhere in these studies that dyspnea is inversely proportional to the vital capacity and directly proportional to the ventilation. Patients with congestive heart failure have diminished vital capacities, and consequently anything which produces marked increase in ventilation tends to cause subjective respiratory distress but only during the time in which the ventilation is increased. Therefore a patient with Cheyne-Stokes respiration and cardiac failure suffers from dyspnea only during the hyperpneic phase and has no distress during apnea. We do not intend to state that dyspnea occurs because of increased ventilation, but we mean to state that both the subjective distress and the augmented breathing are parallel responses (the one cortical and the other medullary) to the same under-

9. Bass and Herr, quoted by Kleitman: Physiol. Rev. **9**:624, 1929. Kunz, J.: Ztschr. f. d. ges. exper. Med. **59**:248, 1928. Endres, G.: Biochem. Ztschr. **142**: 53, 1923.

lying causes, and hence the ventilation may be used at any given level of vital capacity, as a measure of the dyspnea.

The lowered vital capacity is the predisposing cause of the type of dyspnea under consideration, and the increased ventilation is the precipitating factor. It has been shown that the increase in ventilation is a manifestation of periodic breathing, which in turn is a complex phenomenon produced by a combination of a number of factors.

This concept appears to us to account satisfactorily for various clinical phenomena which have been observed, of which the following are examples: 1. Patients with severe congestive heart failure often have repeated "flurries" of dyspnea when awake and then have severe attacks on going to sleep. In those patients overventilation alone may produce Cheyne-Stokes breathing which becomes suddenly worse at the onset of sleep.

2. Patients with less severe congestive failure may have their seizure only on going to sleep. In such instances the overventilation alone is not sufficiently severe to produce marked periodicity, but when the added factor of respiratory depression is present, Cheyne-Stokes breathing becomes pronounced.

3. Attacks of dyspnea of the type under consideration are most common in elderly persons, who are especially subject to arteriosclerotic and hypertensive cardiac disease which impose an initial strain on the left ventricle, and hence lead to overventilation from pulmonary congestion. Furthermore, the sensitivity of the respiratory center is probably less in older subjects with normal hearts, as evidenced by their tendency to periodic breathing.

4. Any stimulus which wakens a patient is likely to precipitate a paroxysm of dyspnea. The sudden increase in respiratory sensitivity as a result of awakening causes overventilation.

5. Once a patient passes the dozing stage and becomes deeply asleep he is likely to have no further periodic breathing. At the onset of sleep the decrease in respiratory sensitivity which tends to precipitate Cheyne-Stokes breathing comes suddenly, but the rise in carbon dioxide tension which is secondary to the diminished ventilation develops gradually and tends to prevent further attacks by abolishing apnea.

SUMMARY

A pneumographic study has been made of patients complaining of attacks of dyspnea coming at the onset of sleep. Such patients exhibit Cheyne-Stokes respiration, which either appears or becomes more marked at the onset of sleep, and later during deep sleep either disappears or becomes less marked. As sleep develops, respiratory periodicity occurs with increasing length of the apneic intervals and a

corresponding increase in the intensity of the hyperpneic phase, which eventually becomes so marked as to awaken the patient and cause dyspnea.

An investigation has been made concerning the underlying factors responsible for these phenomena, and it is concluded that the main causative agents are (1) overventilation due to reflex respiratory stimulation from congested lungs, and (2) respiratory depression occurring at the onset of sleep. Acting singly or in combination these two physiologic alterations appear to be responsible for the periodic breathing. The associated violent hyperpnea in a patient with diminished vital capacity is responsible for the subjective respiratory distress.

Certain observations on the blood gases before and during sleep have been presented, and these are compatible with the hypothesis mentioned. The development of periodic breathing is usually not associated with significant alterations in the composition of the blood. As sleep continues there is, however, a demonstrable increase in the carbon dioxide tension and in the acidity of the blood, and coincidentally the respiration becomes regular.

The alterations in the blood gases are primarily effects of the changes in breathing. However, as a result of the alteration in the blood, the breathing undergoes further changes which lead to the production of the characteristic paroxysmal seizures of respiratory distress.

CONGESTIVE HEART FAILURE

XXI. OBSERVATIONS CONCERNING THE MECHANISM OF CARDIAC ASTHMA

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DEFINITION

The term "cardiac asthma" has been employed by different authors to designate various things. According to certain writers it includes any seizure of paroxysmal dyspnea occurring in a patient with cardiac disease. Other investigators restrict its use to attacks in which at the time of seizure there are auscultatory phenomena similar to those heard in bronchial asthma, i. e., coarse, squeaking, musical or sonorous râles. As used in this and in the future studies of the present series, the term cardiac asthma refers to paroxysms of dyspnea which (1) occur in patients with passive congestion of the lungs secondary to failure of the left side of the heart, (2) usually wake the patient from sound sleep but occasionally occur during the waking hours, (3) sometimes terminate in acute edema of the lungs, (4) are often but not necessarily precipitated by coughing, and (5) are not ordinarily associated with Cheyne-Stokes respiration. In many patients with this condition "asthmatic" râles can be heard over the lungs during the attack. Cardiac asthma does not refer to paroxysmal dyspnea associated with periodic breathing, to dyspnea developing gradually in the afternoon and evening, to attacks of bronchial asthma occurring in persons with right ventricular failure or to acute pulmonary edema appearing as a terminal manifestation in moribund persons without structural cardiac disease.

The various hypotheses which have been advanced to explain the mechanism of cardiac asthma have been reviewed in a previous paper,[1] and it was pointed out that there is no generally accepted theory. It has seemed to us that the results of our observations concerning other kinds of nocturnal dyspnea might serve as a starting point for a further investigation of the subject. All types of cardiac dyspnea which have

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1. Harrison, W. G., Jr.; Calhoun, J. A., and Harrison, T. R.: Congestive Heart Failure: XVIII. Clinical Types of Nocturnal Dyspnea, Arch. Int. Med. **53**:561 (April) 1934.

so far been studied have been shown to be related to two fundamental underlying factors: (*a*) diminished respiratory reserve because of decreased vital capacity and (*b*) reflex stimulation of the respiration. Both of these factors are present during the interval between attacks, for patients with cardiac asthma regularly show both abnormally low vital capacity and abnormally great ventilation. Examples are shown in table 1 of our previous article concerning orthopnea.[2] Subjects Al. C., E. G. and C. M. were studied during attacks of cardiac asthma, and subjects P. H., D. W. and W. J. had attacks, but the observations on them shown in the table were made between seizures. All of these patients had subnormal vital capacities and abnormally great ventilation. Furthermore, the data on the blood gases in the same table indicate that attacks of cardiac asthma are due neither to insufficient aeration of the arterial blood nor to diminished cerebral blood flow, because the three patients mentioned, who were studied during seizures, did not show significant abnormalities either in the arterial blood or in the blood obtained from the internal jugular vein.

Patients with cardiac asthma have pulmonary congestion which has two effects: a decrease in vital capacity and reflex stimulation of respiration. The recent studies of Weiss and Robb,[3] who found that the vital capacity, which was diminished between the seizures, underwent further decline during the attacks, indicate that the degree of pulmonary congestion is increased at the time of the seizures. If we assume, as a working hypothesis, that the underlying cause of cardiac asthma is congestion of the lungs, it is evident that certain questions must still be answered before we can have a clear concept of the mechanism of the syndrome. These include: 1. What is the cause of the greater degree of pulmonary congestion during sleep? 2. What

2. Calhoun, J. A.; Cullen, G. E.; Harrison, T. R.; Wilkins, W. L., and Tims, M. M.: Studies in Congestive Heart Failure. Orthopnea: Its Relation to Ventilation, Vital Capacity, Oxygen Saturation and Acid-Base Condition of Arterial and Jugular Blood, J. Clin. Investigation **10**:833 (Oct.) 1931.

3. Weiss, S., and Robb, G. P.: Cardiac Asthma (Paroxysmal Cardiac Dyspnea), J. A. M. A. **100**:1841 (June 10) 1933. This important study on the subject of cardiac asthma was published since the present article was written. These authors found that the attacks were characterized by an acute increase in the degree of pulmonary congestion. No constant abnormalities in the cardiac output per minute were found either during or between the seizures. Measurements of volume of the lungs revealed a state of acute functional emphysema dependent on engorgement. The vital capacity was decreased during the seizures. Vagal reflexes were demonstrated to be an important factor in the production of dyspnea, which was benefited in several instances by blocking the vagus nerves with procaine hydrochloride. The essential mechanism of the seizures was believed to be the coexistence of subacute left ventricular failure and acute precipitating factors. Our conclusions are, in general, in accord with those of Weiss and Robb.

is the relation between cardiac asthma and acute pulmonary edema? 3. Why do many patients with cardiac asthma exhibit auscultatory phenomena similar to those heard in bronchial asthma? 4. Why does morphine have a beneficial action in preventing and combating the seizures? The following studies were carried out to gather data concerning these questions.

RESULTS

Effect of Morphine on Respiratory Measurements and on Blood Gases in Patients with Cardiac Asthma.—In order to determine whether or not there was an increased degree of pulmonary congestion during the seizure we made attempts to measure the vital capacity and the ventilation during and after the attack. In order to be certain that the two observations could be made within a short time of each other morphine was given immediately after the first studies had been made, and the investigations were repeated from thirty to forty minutes after administration of the drug; by that time the patient's dyspnea had usually diminished or disappeared. Measurements of ventilation and of vital capacity were made, and in addition samples of arterial blood were obtained and analyzed by the methods used in the other studies of this series (carbon dioxide and oxygen with the Van Slyke apparatus, p_H by Cullen's method and carbon dioxide tension by calculation from the Hasselbach formula, using a value of 6.1 for pK^1).

The data are shown in table 1. During the seizure the vital capacities were considerably lower and the ventilation much greater than normal. We have repeatedly measured the resting ventilation per minute of normal subjects under similar conditions and have found values ranging from 3.5 to 6 liters, whereas, during the seizures of cardiac asthma the values for the patients were between 7.4 and 14.1 liters per minute. Similarly, normal adults usually have vital capacities of from 3 to 5 liters, whereas the vital capacities of the patients were usually considerably less than this.

Following the administration of morphine six of the seven subjects experienced relief, relative or absolute, from dyspnea. In each of the six there was a well marked decrease in ventilation. The seventh patient said that his dyspnea was no better, and he failed to show any decrease in ventilation. This patient's vital capacity was lower after he had received morphine; three subjects exhibited a definite although slight increase in vital capacity, and two subjects exhibited no significant change in this function. The latter two passed into a state of sound sleep after receiving morphine and had to be aroused repeatedly in order that vital capacities might be measured.

During the dyspneic seizure the respirations were usually faster than normal, and in every case the rate of breathing was slower after

medication, this effect being least pronounced in the patient J. P. whose subjective distress was not relieved.

Analyses of the arterial blood taken during the attack of dyspnea revealed no constant abnormalities. One patient who also had acute pulmonary edema had marked anoxemia, and this man's arterial satura-

TABLE 1.—*Effect of Morphine on Blood Gases and on Respiratory Movements*

Subject	Date, 1931	Conditions	Oxygen Saturation, per Cent	Serum Carbon Dioxide, Volumes per Cent	Serum Carbon Dioxide Tension Mm. of Mercury	Serum p_H	Vital Capacity, Liters	Ventilation per minute, Liters	Ventilation / Vital Capacity	Respiration per Minute	Comment *
J. D.	10/15	Before morphine	100.0	59.7	39.0	7.43	2.04	14.1	6.91	48	Dyspnea, severe
		After morphine	99.3	62.8	42.7	7.42	2.10	11.6	5.50	25	
E. G.	10/15	Before morphine	92.8	51.4	26.9	7.54	2.49	13.4	5.38	33	Dyspnea, severe
		After morphine	91.9	52.5	36.5	7.41	2.65	9.9	3.72	17	
W. L.	11/ 2	Before morphine	56.4	74.0	44.1	7.48	....	10.5	....	31	Acute pulmonary edema
		After morphine	80.1	73.3	41.8	7.50	....	7.8	....	27	Dyspnea, very severe
B. S.	12/15	Before morphine	92.4	54.8	40.7	7.38	2.24	10.1	4.52	15	Dyspnea, mild
		After morphine	92.0	56.1	40.9	7.39	2.37	8.5	3.59	12	
S. U.	12/19	Before morphine	....	60.0	43.6	7.39	3.30	7.4	2.26	23	Dyspnea, mild; venous blood
		After morphine	....	57.4	41.7	7.39	3.48	5.5	1.59	15	Dyspnea, mild; venous blood
M. G.	12/19	Before morphine	....	....	....	....	2.08	12.7	6.11	26	Dyspnea, moderate
		After morphine	....	....	....	....	2.05	6.7	3.26	20	
J. P.	12/30	Before morphine	86.0	66.2	44.2	7.45	1.90	10.2	5.38	17	Dyspnea, severe
		After morphine	84.0	67.2	43.9	7.44	1.70	10.1	5.94	15	Not helped by morphine

* In all the patients except in the last one the dyspnea was less severe after morphine had been administered.

tion rose from 56 per cent before to 80 per cent after the administration of morphine. The other patients had values ranging from 100 to 86 per cent for the arterial oxygen saturation during the paroxysm, and relief from the dyspnea by morphine was not associated with significant changes.

Similarly, the values for carbon dioxide content of the arterial serum were all within normal limits during the dyspneic seizure and were not

altered in any constant direction by morphine. In five patients the p_H was likewise within the normal range during the attack; the sixth had a tendency toward alkalosis (p_H 7.54). In the last subject relief from dyspnea by morphine was associated with a decrease of 0.13 in p_H and an increase of approximately 10 mm. in carbon dioxide tension. Other subjects exhibited no significant changes in p_H after they received morphine. Likewise the carbon dioxide tension exhibited no constant alterations, the only striking change being in the subject mentioned who had, during the paroxysm, an abnormally low carbon dioxide tension, whereas the values for the other patients were within the normal range.

It is evident from these data that the dyspnea of cardiac asthma cannot be primarily attributed to insufficient aeration of the arterial blood, although anoxemia may be an important added factor when acute pulmonary edema supervenes. Except in patients with pulmonary edema, morphine does not usually produce significant changes in the composition of the arterial blood. Occasionally, relief from dyspnea may be associated with decided increase in the acidity of the blood.

These conclusions are in general agreement with those of other authors. Eppinger, von Papp and Schwarz [4] found that their dyspneic patients usually had normal values for carbon dioxide pressure and p_H, whereas anoxemia of marked degree occurred only in subjects with edema of the lungs or other pulmonary disorders. Fraser [5] reported low values for carbon dioxide tension and hydrogen ion concentration of the arterial blood in the majority of his dyspneic patients, but noted that patients with pulmonary edema had anoxemia. He likewise studied patients before and after the administration of morphine and observed that in some instances this drug, although relieving the dyspnea, caused the carbon dioxide tension to increase and the oxygen saturation to decrease.

It appears, therefore, that the precipitating causes of the attacks of cardiac asthma do not act by altering the composition of the blood but by influencing the vital capacity and the ventilation.

Importance of cough as a Precipitating Cause of Paroxysmal Dyspnea.—Patients with paroxysmal cardiac dyspnea may be classified in three groups with regard to their cough: 1. Subjects who have characteristic paroxysmal nocturnal dyspnea with little or no cough. With this group of patients we are not, for the present, concerned.

4. Eppinger, H.; von Papp, L., and Schwarz, H.: Das Asthma cardiale, Berlin, Julius Springer, 1924.

5. Fraser, F. R.; Harris, C. F.; Hilton, R., and Linder, G. C.: Quart. J. Med. **22**:1, 1928.

2. Patients who state that they wake up and feel short of breath and later begin to cough, thereby becoming more short of breath.

3. Persons who have coughing "spells" and then begin to feel dyspneic. The paroxysms may occur when the subject is awake but are likely to be more severe during the night, awakening the patient from sleep. Patients in this group insist that while at rest they have no dyspneic seizures other than those which are preceded by coughing. Observation during the attacks confirms their statements. While breathing quietly they begin to cough and after cessation of the cough the respirations remain rapid and labored for a time and then gradually return to the previous rate and character. During and immediately after the coughing seizure striking venous distention and outspoken cyanosis may develop.

The following cases are illustrative of the importance of cough as a precipitating factor in causing attacks of paroxysmal dyspnea.

CASE 1.—M. S., a white housewife, aged 63, suffered from frequent attacks of bronchitis for many years. Dyspnea on exertion had been progressive during the past ten years, and for five years she had had occasional paroxysms of coughing in the day and, during the night, frequent severe seizures which would wake her from a sound sleep. After the coughing began she would feel short of breath. Eventually she would expectorate a small amount of mucopurulent sputum, and her coughing would cease abruptly but her dyspnea would last for a number of minutes longer, then gradually decrease and finally disappear. For three months there had been progressive swelling of the feet and abdomen.

Examination revealed undernurtition, marked cyanosis, slight clubbing of the fingers, venous distention, moderate cardiac enlargement to the right and left, an accentuated second sound in the pulmonic area and typical signs of emphysema, bronchitis and bronchiectasis. There was no orthopnea. The liver was markedly enlarged and there were signs of free fluid in the abdomen. The electrocardiogram revealed right ventricular preponderance. The patient was observed for ten days in the hospital and during this period never complained of dyspnea except during or after a paroxysm of coughing. Every attack of coughing which lasted for more than a few seconds was accompanied by some dyspnea. There were mild seizures during the day, but the most severe attacks came at night after she had been asleep for two or three hours.

This patient showed a typical case of cardiac failure secondary to chronic pulmonary disease (cor pulmonale, pulmonary hypertension). Her dyspneic seizures were due to her cough. However, she could not be considered as having cardiac asthma because clearly her dyspnea was originally of pulmonary origin, and cardiac failure developed secondarily.

CASE 2.—M. G., a Negress, aged 42, was first seen in July, 1928, complaining of cough and of paroxysmal dyspnea which would wake her from a sound sleep. At this time she was found to have hypertension, marked cardiac enlargement, gallop rhythm, and a few râles at the bases of the lungs. Following medication

with digitalis and no other treatment, she became free from symptoms and remained so for two years, except for dyspnea on climbing stairs and some nocturnal seizures during very hot weather. During the last two years her cough had become much worse. In December, 1931, she had a second frank break in compensation and had to be readmitted to the hospital. Her blood pressure was still elevated. There were scattered dry, piping râles throughout both lungs and moist râles at the bases of the lungs. She was observed during the attacks of dyspnea; these sometimes came on during the late afternoon or early evening while the patient was awake, particularly when the room was unusually warm, but usually they occurred after she had been asleep for an hour or more.

While still asleep she would begin to cough and then, on awakening, the cough would become more violent, and she would complain of dyspnea. Her seizures always began with cough, and during the attacks there would be a greater number of moist and dry râles in the lungs. Morphine always gave relief.

In this patient hypertension caused pulmonary congestion which later was complicated by bronchitis. Coughing precipitated her attacks of dyspnea. The majority of patients with cardiac asthma present clinical pictures somewhat similar to this one.

CASE 3.—J. P., a Negro, aged 49, began to have dyspnea on exertion six months before admission. One month later he began to have attacks of paroxysmal dyspnea at night; these usually started after 8 p. m., lasted thirty or forty-five minutes, were usually preceded by a "rattling or wheezing" in the throat and often by a severe attack of coughing. During this time the patient would sit upright, cough, become quite dyspneic and spit up tenacious sputum. After a number of minutes the attacks would cease. Gradually the seizures became more frequent, and for the past two weeks they had troubled him much more than usual. He had slight palpitation during the attacks. There had been no edema of the ankles and no precordial pain.

Examination revealed a tall, thin, but well developed Negro, who could lie flat in bed without dyspnea at the time. The lungs showed numerous coarse, scattered râles over the middle of each side of the chest in the back. These tended to clear after cough. The heart was enlarged and the rate increased; the sounds were forceful, and infrequent extrasystoles were present. The second aortic sound was accentuated. A faint, early blowing diastolic murmur was heard down the middle of the sternum and at the apex, where there was also a presystolic gallop. The pulse was rapid and full, not definitely of the Corrigan type. The blood pressure was 146 systolic and 92 diastolic, and pulsus alternans was noted. The liver was not felt, and there was no pitting edema. The Wassermann reaction was positive. A diagnosis of syphilis of the aorta with aortic insufficiency was made.

While in the ward the patient had several attacks of paroxysmal dyspnea. His chest had been examined immediately before one of these attacks, and at that time his lungs were clear. He was lying in a semirecumbent position and was only slightly short of breath. In order to observe the effects of coughing a face mask was attached, and after several minutes, during which the expired air was collected, he was instructed to cough violently. Within two minutes after he had started coughing he suddenly sat straight up in bed, became markedly dyspneic, broke out in profuse perspiration, continued to cough and expectorated a moderate amount of frothy sputum; after about ten minutes the attack gradually ceased. During

the attack moist râles were audible throughout the lower portion of the chest, but these soon cleared up. Under rest in bed, medication with digitalis and sedatives the attacks ceased and he improved.

This patient illustrates the effect of cough in producing marked dyspnea associated with the sudden development of pulmonary edema.

In order to obtain objective data concerning the effect of coughing on breathing the ventilation was measured in a number of patients before, during and after coughing. For this purpose a face mask and a Tissot spirometer were used. The patient sat quietly in a comfortable chair for fifteen minutes or longer, and the face mask was then applied. After a further preliminary period the resting ventilation was measured for three successive minutes. The subject was then instructed to cough every ten seconds. This was kept up for three minutes. During the

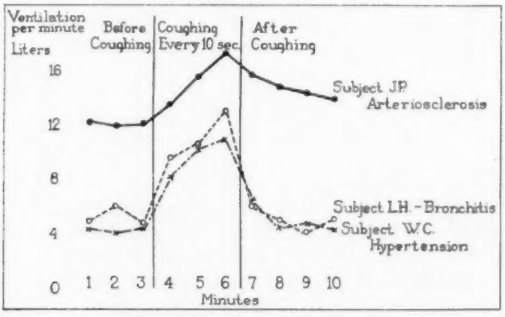

Fig. 1.—The upper curve represents the ventilation of a patient with mild congestive heart failure; the two lower curves are from patients who were ambulatory and free from symptoms at rest but had some dyspnea on exertion. Voluntary coughing produced an increase in the ventilation in each subject, caused slight dyspnea in L. H. and W. C., and resulted in marked dyspnea in the case of J. P., who was already slightly dyspneic before coughing. After coughing had ceased the ventilation of the two patients with compensation returned to normal rapidly, but the ventilation of the patient with decompensation remained elevated for several minutes. The curves showing the effect of coughing on the ventilation are similar to other curves obtained following any type of muscular exertion in patients with cardiac disease.

coughing and for the subsequent four minutes after coughing had ceased further measurements of ventilation were made.

In figure 1 are plotted examples of the results obtained. The upper curve represents data on a subject with decompensation who was slightly short of breath at rest. The two lower curves are obtained from ambulatory subjects who had dyspnea on walking rapidly but not at rest. It is to be noted that coughing caused a marked and progressive

rise in ventilation in each patient. L. H. and W. C. both felt slightly short of breath during and immediately after coughing. J. P., who was already slightly dyspneic at rest, complained of marked respiratory distress during and for several minutes after coughing. It is to be noted that the ventilation of the ambulatory patients remained above the resting level for about a minute after coughing stopped while the respiratory minute volume of the patient with decompensation was still elevated four minutes after the cessation of coughing.

In figure 2 are shown respiratory tracings from a normal subject and from two patients with congestive cardiac failure. Following voluntary coughing for one minute the normal person had a slight increase in respiratory rate which gradually returned to normal. In both of the patients the coughing was involuntary, coming on in one subject following a deep breath and beginning spontaneously in the other patient. It is to be noted that the increase in respiratory rate was much more pronounced in both patients who experienced dyspnea during and after the coughing than in the normal subject who experienced no dyspnea.

It is a common clinical experience that a deep breath, particularly if associated with forced expiration, is likely to be followed by coughing. In measuring vital capacities one frequently finds that each maximal expiration is followed by a short paroxysm of coughing, which is often attended and followed by an increase in the degree of preexisting dyspnea. These events are illustrated by figure 3. All of the tracings were made from the same patient, a man with congestive cardiac failure secondary to syphilitic aortic insufficiency. A maximal inspiration followed by a maximal expiration resulted in coughing, rapid breathing and dyspnea. His respiratory distress gradually subsided, and a few minutes later the respiratory rate was the same as at the beginning of the observations. A deep breath again precipitated coughing and dyspnea. He was then given 0.015 Gm. of morphine subcutaneously, and fifteen minutes later the observations were repeated. In this instance deep breathing did not initiate coughing; the respirations did not become accelerated, and no dyspnea developed. Morphine, by depressing the reflex excitability, had broken the vicious cycle.

The foregoing histories of cases and respiratory curves indicate that in certain patients with congestive heart failure coughing plays an important rôle in initiating seizures of paroxysmal dyspnea and that in other patients who are already dyspneic coughing increases the degree of respiratory distress. These facts are readily explainable when one remembers that patients of this type nearly always suffer from dyspnea on the performance of muscular exercise, and that a cough is a rather violent muscular effort. In a preceding study of

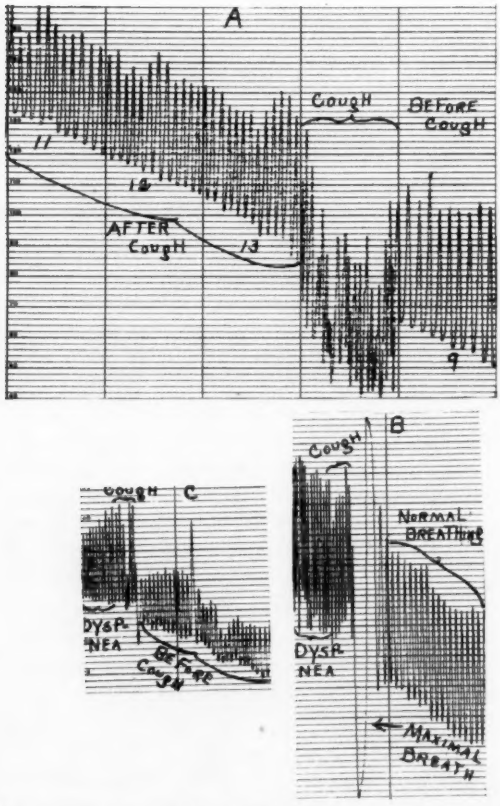

Fig. 2.—The curves all pass from right to left. The distance between two adjacent vertical lines represents one minute. The numbers below the tracing in part *A* refer to respiration per minute. The upper tracing (*A*) was obtained from a normal subject who was instructed to cough for one minute. A well marked increase in respiratory rate and a slight temporary increase in depth of breathing occurred after cessation of the cough. The lower tracing on the right (*B*) illustrates involuntary cough as a result of a deep breath and maximal expiration in a patient with mild congestive cardiac failure. Following the coughing there was a marked increase in breathing, and the subject felt short of breath. The lower tracing on the left (*C*) was made from a patient with mild congestive cardiac failure during a mild seizure of nocturnal dyspnea. The cough occurred spontaneously, and immediately afterward there was a marked increase in the rate and depth of breathing, with rather severe dyspnea.

the present series [6] it was shown that muscular movements cause reflex stimulation of breathing. Hence, in this way cough tends to produce dyspnea. Furthermore, the act of coughing may cause a rather great temporary increase in consumption of oxygen (as much as 50 per cent in some of our cases) and this would obviously tend to increase the work of the heart and hence to aggravate the underlying condition responsible for the dyspnea.

However, there is another effect of cough which is probably even more important. In the previous study which has been referred to it was shown that increase of pressure in the right auricle and in the cardiac ends of the great veins caused reflex stimulation of breathing. Any form of muscular exercise probably tends to cause a rise in venous

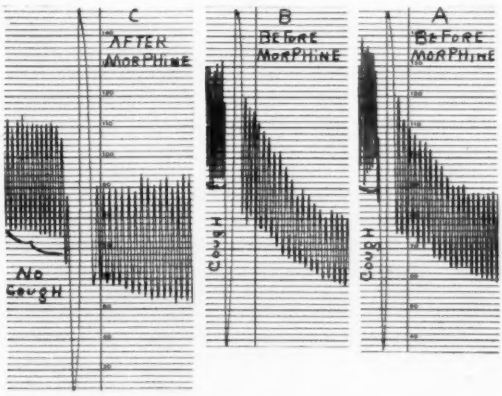

Fig. 3.—The curves pass from right to left. All of the tracings were made from the same patient, a man with congestive heart failure and nocturnal dyspnea. The right (*A*) and center (*B*) curves illustrate the occurrence, following a deep breath, of cough and increased breathing which were associated with dyspnea. Morphine was administered, and a few minutes later another tracing was made. A deep breath no longer caused coughing. The respirations did not increase, and the patient felt no dyspnea.

pressure, but coughing is especially important in this regard because during coughing there is a rise in the intrathoracic pressure with resulting distention of the extrathoracic veins. Hence, at the beginning of each inspiration following coughing there is a sudden inflow of blood into the right auricle with a resultant rise of pressure in that chamber.

6. Harrison, T. R.; Harrison, W. G.; Calhoun, J. A., and Marsh, J. P.: Heart Failure: XVII. The Mechanism of Congestive Dyspnea on Exertion, Arch. Int. Med. **50**:690 (Nov.) 1932.

Probably because of this fact coughing has a greater effect on breathing than other muscular effort of comparable degree.

Furthermore, it has been shown [6] that a given muscular effort produces a greater rise in venous pressure and in ventilation in a person with congestive heart failure than in a normal subject. That this is true of the muscular effort of coughing is illustrated in figure 2, in which it can be seen that the degree of increase in respiratory rate following coughing was much greater in the two patients than in the normal subject.

It is also possible that the mechanical effect of coughing may be such as to interfere with exchange of gas in the lungs and hence to add a chemical factor to the reflex influence tending to produce dyspnea. We have made no observations on this point.

As has been stated, the paroxysms of cough may come in the day but are more likely to begin during sleep and to wake the patient. One reason for this seems obvious. If, owing to pulmonary congestion, bronchitis or both conditions, there is an increase in the amount of bronchial secretion, the patient is likely to expectorate it in small amounts at frequent intervals during the day, each expectoration being accomplished by a short fit of coughing. During sleep, on the other hand, the reflex irritability of the nervous system is depressed, and consequently a greater amount of mucus accumulates before the cough reflex is elicited. However, once coughing begins, it wakes the patient, and the waking is associated with an increase in reflex irritability. Hence, the cough becomes severe and causes an increase in ventilation which, in a person whose respiratory reserve (vital capacity) is already low, is associated with dyspnea. The sequence of events in such instances is similar to that which occurs in any disease associated with cough and expectoration in persons who do not have cardiac disease, the only difference being that the latter subjects are less likely to have dyspnea because their vital capacities are greater and also because coughing does not, for the reasons already mentioned, cause as great an increase in ventilation in such persons as in subjects who have congestive heart failure. However, the difference is qualitative only, for severe paroxysms of cough such as occur in whooping cough, for instance, may cause dyspnea in persons who have normal hearts. In the case of the patient with congestive heart failure it requires less coughing, just as it requires less walking, to produce dyspnea.

It was pointed out (figs. 2 and 3) that, not only does coughing increase the breathing, but that deep breathing, especially forced expiration, tends to bring about coughing. Thus a vicious cycle may develop. the patient's attack beginning with either dyspnea or cough, and each symptom aggravating the other, the situation becoming continually

worse unless relieved either by the administration of a sedative or by expectoration of mucus.

The results obtained by measures which suppress the cough offer a further illustration of the importance of this "trigger" factor. We have occasionally seen paroxysmal dyspnea of the type in question benefited by inhalations of steam and have often seen the attacks abolished by cough syrups containing codeine, although in severe cases morphine may be necessary.

Other Precipitating Causes of Paroxysmal Dyspnea.—Cough has appeared to be the most common and most important of the precipitating causes of the dyspneic attacks in the majority of our patients. However, it is not the only factor which may start the seizures. During the patient's waking hours any stimulus which increases the ventilation

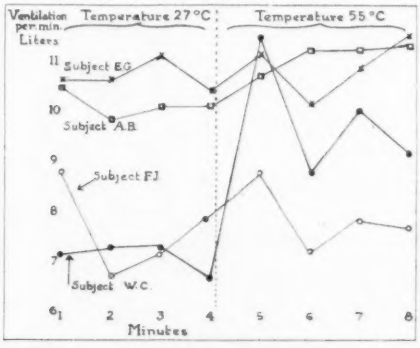

Fig. 4.—The subject rested on a couch in a warming cabinet. The ventilation was first determined at room temperature (27 C.), and then the temperature of the cabinet was increased to 55 C. by means of electric lights. The head remained outside of the cabinet. Two of the subjects showed a definite increase in ventilation, whereas the remaining two did not. This inconstancy of response is in keeping with the fact that heat is a precipitating cause of cardiac asthma in some persons and not in others.

may initiate an attack of dyspnea. Such stimuli are doubly effective if they happen to awaken the patient from sleep because then there is the added factor of the sudden increase in the sensitivity of the nervous system (and hence of the respiratory center) which occurs on passing from the sleeping to the waking state. In our patients attacks of cardiac asthma have been precipitated by such widely varying factors as nightmares, hunger, very hot weather, abdominal distention, constipation and the desire to urinate. Observations concerning the effects of some of these stimuli on breathing have been made, and examples of the results are shown in figures 4, 5 and 6. The action of an increase in

the environmental temperature was studied by placing the patient in a warming cabinet and, after measuring the ventilation at room temperature, repeating the observations with the temperature of the cabinet increased to 55 C. The head remained outside of the cabinet. As can be seen in figure 4, some persons reacted with an increase in ventilation while others did not.

The effect of fear was studied by making noises, breaking glassware, dropping tin pans on the floor, etc., while the ventilation was being measured. In figure 5, it is shown that apprehension caused a well marked increase in the ventilation in each of four subjects. It seems probable that nightmares, associated as they are with severe apprehension, have a similar effect on breathing. Such an increase in ventilation in a patient who, because of congested lungs, is already at the threshold of dyspnea will result in respiratory distress.

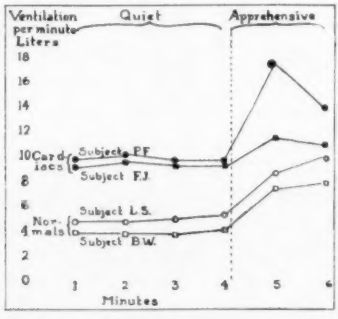

Fig. 5.—After the ventilation had been measured during resting conditions the subject was frightened by noises which were produced by slamming doors, breaking glassware and dropping tin pans on the floor, and by altercations between the operators. All the subjects remained at rest but each showed well marked increase in ventilation, and at the end of the observation each admitted that he had been frightened by the noises. It is assumed that unpleasant dreams have a similar effect on ventilation.

In order to learn something concerning the effects of distention of abdominal viscera on respiration, experiments have been made on dogs. It has been found that some animals react regularly with faster breathing and increased ventilation to the introduction of fluid into the bladder or into the rectum. Other dogs have shown less constant effects. Examples of the type of results which have been obtained are shown in figure 6. It can be seen that the introduction of 50 cc. of saline solution into the bladder caused a definite increase in respiration. Similar effects were produced in another animal by distending the colon with 100 cc. of barium sulphate paste. Up to the present time

the observations are incomplete, as the afferent path of the reflex which is probably concerned has not yet been determined. Complete observations along this line will be published at a later date, but it seems justifiable to conclude at present that distention of the bladder or colon may produce an increase in breathing.

Relation of Acute Pulmonary Edema to Cardiac Asthma.—Any attempt at a satisfactory understanding of the pathogenesis of cardiac asthma necessarily involves an explanation of the mechanism of acute edema of the lungs, which is an integral and fearsome feature of the seizures in many patients. That the underlying cause of acute pulmonary edema is failure (i. e., dilatation) of the left side of the heart is clearly indicated by the observations at necropsy in such cases, as well as by the classic experiments of William H. Welch,[7] who produced acute

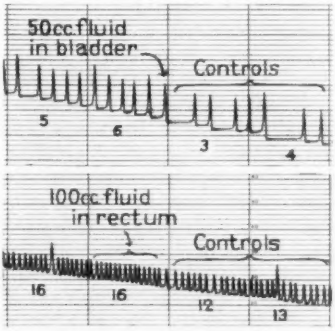

Fig. 6.—The distance between two adjacent vertical lines indicates one minute. The curves, which pass from right to left, represent spirometric tracings on a dog. In this animal a consistent but rather slight increase in respiration was produced either by distending the rectum with bismuth paste or by distending the bladder with saline solution. These effects have been found in the majority but not in all of the animals studied.

edema of the lungs in rabbits by compressing the left ventricle. However, one has to explain why it is that while the strain on the left side of the heart is constantly present in these patients, the onset of pulmonary edema occurs in sudden seizures. In this regard the suggestion of Fraser,[5] that an increase in respiratory movements incident to the dyspneic seizure might lead to a further increase in pulmonary congestion, has seemed to merit study. According to this hypothesis the effect of an increase in ventilation would be to cause an increased venous return and hence a greater cardiac output. If because of overwork and disease the left ventricle were less able than the right to

7. Welch, W. H.: Virchows Arch. f. path. Anat. **77**:375, 1878

perform this added work, more blood would accumulate in the already congested lung. In an attempt to determine whether or not this hypothesis is correct further observations have been made.

1. Effect of Increased Respiratory Movements on the Cardiac Output: It is possible under certain conditions to determine qualitative changes in cardiac output by measuring the absorption of oxygen. Since the amount of oxygen consumed by the lungs themselves is so small as to be negligible, it is evident that all of the oxygen which is removed from the inspired air passes into the blood. Over any period of minutes or longer, the amount of oxygen passing into the venous blood in the lungs is equal to and determined by the amount of oxygen passing from the arterial blood in its transit through the tissue capillaries. However, any sudden increase in the amount of blood passing through the lungs must be immediately reflected by a similar increase in the amount of oxygen absorbed unless the amount of oxygen in the arterial blood is to undergo diminution. As this excess blood passes through the tissues, less oxygen will be removed, and the venous blood, returning richer in oxygen, will absorb less oxygen per unit of blood than before. Hence, even though the flow of blood through the lungs remains elevated, the intake of oxygen will tend to return to normal after recirculation has occurred, but before recirculation has taken place, changes in the absorption of oxygen will afford a measure of the changes in flow of blood through the lungs, i. e., of changes in the cardiac output.

The filling of the heart is dependent on the "effective venous pressure," i. e., on the difference between the pressure in the veins and that in the right auricle, which in turn is affected by the intrathoracic pressure. Under ordinary conditions one would expect an increase in ventilation to diminish the average pressure in the chest cavity (i. e., to make this pressure more negative), and hence, if other things remained equal, the degree of cardiac filling should be greater with a resultant increase in the cardiac output and in the pulmonary flow of blood, which would cause an increase in absorption of oxygen during the time required for one circulation of the blood to occur. That these events actually do take place in normal persons as a result of overventilation is indicated clearly by the fact that the consumption of oxygen is increased during the determinations of cardiac output by the Krogh-Lindhard, Grollman and similar methods, which necessitate an increase in the respiratory movements for periods of from fifteen to twenty seconds. There is some question, however, as to the ability of the cardiac output to increase in a person who has congestive heart failure. In order to test the matter the observations shown in table 2 were made. Under resting conditions the ventilation and consumption of oxygen were determined by means of a face mask, a Tissot spirometer and analysis with the

Haldane apparatus. The subject was then instructed to increase his ventilation, and the consumption of oxygen was determined during the first fifteen or twenty seconds of the overventilation and during subsequent periods. Any immediate rise in consumption of oxygen could be

TABLE 2.—*Immediate Effects of Overventilation on Intake of Oxygen*

Subject	Date	Conditions	Ventilation per Minute, Liters	Intake of Oxygen per Minute, Cc.	Excretion of Carbon Dioxide per Minute, Cc.	Respiratory Quotient
Normal subject W. G. H.	3/18	Rest	4.52	180	146	0.81
		Maximal overventilation				
		1st 15 seconds	84.4	1,715	1,545	0.90
		2d 15 seconds	64.2	497	892	1.79
	3/24	Rest	5.23	166	180	1.08
		Maximal overventilation				
		1st 40 seconds	74.6	638	1,200	1.87
		40th to 60th second	57.0	497	826	1.66
Normal subject J. A. C.	3/25	Rest	3.97	169	140	0.83
		Moderate overventilation				
		1st 20 seconds	33.5	436	686	1.57
		2d 20 seconds	29.4	399	632	1.59
		3d 20 seconds	29.0	293	476	1.63
	3/28	Rest	3.95	179	160	0.90
		Moderate overventilation				
		1st minute	22.2	512	634	1.24
		2d minute	20.6	278	497	1.68
	3/28	Rest	3.98	179	160	0.90
		Moderate overventilation				
		1st 2 minutes	20.4	402	539	1.34
		2d 2 minutes	18.1	300	432	1.44
	3/25	Rest	4.35	211	173	0.82
		Mild overventilation 1st 20 seconds	20.4	505	661	1.31
		Moderate overventilation (after intervening period of rest for 15 minutes)				
		1st 20 seconds	44.7	967	1,228	1.27
Subject with cardiac failure W. C.	3/22	Rest	5.10	201	178	0.89
		Maximal overventilation				
		1st 15 seconds	18.5	509	508	1.00
		2d 15 seconds	17.0	294	333	1.13
	3/23	Rest	5.43	192	165	0.86
		Maximal overventilation				
		1st 10 seconds	22.2	511	540	1.06
		10th to 30th second	25.0	403	448	1.11
Subject with cardiac failure P. F.	3/24	Rest	10.5	273	245	0.90
		Maximal overventilation				
		1st 20 seconds	33.1	544	611	1.12
		2d 20 seconds	32.0	322	421	1.31

due only to an augmented cardiac output, whereas, a delayed rise would be attributable to a true increase in tissue metabolism as a result of the greater muscular activity incident to the augmented respiratory movements.

Six observations were made on two normal subjects, and three tests were done on two patients with cardiac disease. The different experi-

ments varied in the intervals of time used and in the degree of overventilation employed. The various subjects showed somewhat different quantitative responses, but the qualitative effect of the overventilation was the same in all instances. Each time there was a striking immediate rise in the consumption of oxygen during overventilation. Later, although the increased breathing continued, consumption of oxygen declined markedly but remained well above the resting level as long as the increased ventilation was maintained. Regardless of the intervals of time employed, the absorption of oxygen always took place at a faster rate during the first than during the latter part of overventilation. The patients with cardiac failure who were not able to overventilate as much as were the normal subjects showed similar but less marked initial increases in absorption of oxygen. Furthermore, in a given subject on a given date there was a parallelism between the degrees of increase in consumption of oxygen and in ventilation (table 2, subject J. A. C., March 25, 1932).

These results seem to admit of only one interpretation, i. e., that increasing the ventilation causes an increase in cardiac output, not only in normal persons but in persons with cardiac failure.[8]

2. Effect of Increased Respiratory Movements on the Vital Capacity: The observations which have just been reported indicate that the amount of blood passing through the lungs is increased when the ventilation is increased. In a person with normal relationships of pressure in the lesser circulatory system one would not expect such a change to cause congestion of the lungs, but the result might be quite different in a patient in whom there existed an impediment to the escape of blood from the lungs because of "back pressure" from a dilated left ventricle. Direct measurements of the amount of blood in the lungs of patients are not possible, but the vital capacity constitutes a guide to qualitative alterations in the degree of pulmonary congestion. Consequently we have made comparisons of the vital capacity as determined immediately after normal breathing with that measured following one minute of moderate—not maximal—overventilation. In each subject from three to five such comparisons were made, the vital capacity being recorded graphically for the sake of accuracy in measurement.

Examples of the results are shown in figure 7. Normal subjects showed a definite tendency to have higher vital capacities following overventilation, a finding which is probably to be interpreted as indicating that the volume of blood in the lungs was somewhat diminished by the increased respiratory movements. In view of the

8. Since this paper was written our attention has been called to the study of Grollman (Am. J. Physiol. **94**:287, 1930), who observed an increase in the cardiac output of normal men during overventilation.

spongelike structure of the lungs such a result is not surprising. Patients with cardiac failure usually—but not always—exhibited some slight diminution in vital capacity following overventilation. This effect, which was the reverse of that observed in normal persons, apparently indicates that when there is obstruction to the outflow of blood from the lungs (left ventricular failure) an increase in the venous return will tend to cause greater pulmonary congestion.

It appears, therefore, that the increased ventilation produced by any of the causes which have been mentioned may in itself become a further cause of pulmonary congestion and hence initiate a vicious cycle. It is true that the decrease in vital capacity which occurred in our patients as a result of overventilation was of slight degree, being usually not more that 100 cc. However, in one patient voluntary over-

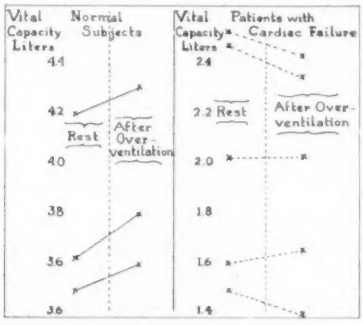

Fig. 7.—Each point represents an average value for from three to five measurements of vital capacity. In the normal subjects voluntary overventilation for one minute was followed by a slight increase in this function. The patients with cardiac disease showed no constant effect, although the vital capacity was slightly lower in three of the five subjects. It is possible that the other two persons would have reacted similarly, had the overventilation been maintained for a longer time. In a sixth patient acute edema of the lungs developed following voluntary overventilation. During the attack the vital capacity apparently decreased about 25 per cent, but since the accuracy of this measurement is questionable the values for this patient were not included in the figure.

ventilation produced a typical seizure of cardiac asthma which was accompanied by acute pulmonary edema and was so severe as to render accurate measurements of vital capacity impossible.

This patient, a Negress, aged 49, with cardiac failure secondary to hypertension, was having frequent attacks of paroxysmal dyspnea which awakened her from sleep and which always followed coughing. At a time when she was free from dyspnea, observations were made concerning the effect of overventilation on her vital capacity. Following voluntary increase in respiratory movements for one-half minute, she began to cough and was short of breath for several minutes

thereafter. A quarter of an hour later she was quite comfortable again, and the procedure was repeated with similar results. Following a third period of voluntary overventilation for one minute she became excessively dyspneic, had to sit upright and hang her legs over the bed; she coughed violently, broke out into profuse perspiration, began to tremble, developed muscular twitchings and expectorated frothy sputum. The vital capacity measured at this time was about 25 per cent less than it had been when measured following quiet breathing a few minutes before. (No tracing from this patient was included in figure 7 because the accuracy of the value obtained under such conditions was considered questionable.) During the seizure of dyspnea moist râles, which had not been present previously, could be heard over the bases of both lungs. For several minutes the patient presented all the signs of a severe attack of pulmonary edema. The administration of morphine was followed by relief within a short time.

Furthermore, in a previous paper [9] it was shown that in a dog the respiratory rate may be markedly affected by the introduction of as little as 25 cc. of blood into the lungs, and hence it was concluded that a barely measurable decrease in vital capacity might, if produced by pulmonary congestion, cause pronounced respiratory stimulation. This in turn would lead to further congestion, and so on. The administration of morphine would tend to break the vicious cycle because of the diminished respiration with the resulting decreased inflow of blood into the lungs and diminished pulmonary congestion (table 1). Fraser [5] believed that this was the mechanism whereby morphine produced improvement in patients with cardiac asthma, and our data are in support of this suggestion.

In many patients the attacks of dyspnea subside spontaneously without morphine or other sedatives. The expectoration of mucus and the consequent relief of cough have apparently been responsible for the spontaneous termination of the attack in a number of patients. Likewise, the milder cases have frequently been relieved by the assumption of a more nearly upright posture, in which the vital capacity is greater. In other instances, urination, belching or bowel movements have produced relief by abolishing the precipitating cause of the attack. Possibly the depressant effect on respiration of loss of carbon dioxide from overventilation may predominate in some patients over the reflex respiratory stimulation due to the pulmonary congestion. Concerning this point we have no data, as our patients have received morphine whenever the attack was severe and not relieved in a short time by one of the procedures already mentioned. On the other hand, if the latter factor predominates, the lungs, which were congested before the onset of the attack, should become progressively more engorged during the seizure. Because of their loose structure it is

9. Harrison, W. G., Jr.; Calhoun, J. A.; Marsh, J. P., and Harrison, T. R.: Congestive Heart Failure: XIX. Reflex Stimulation of Respiration as the Cause of Evening Dyspnea, Arch. Int. Med. **53**:724 (May) 1934.

probable that a great quantity of blood may accumulate in the lungs without causing marked rise in the pulmonary capillary pressure. Eventually, however, as the congestion becomes more severe, this pressure will rise, at first slowly and then more rapidly. Once the limits of elasticity are approached, the further addition of a small amount of blood will cause a marked rise in pressure (fig. 8). Such a series of events will, if unchecked, result in edema of the alveolar spaces when the pulmonary capillary pressure has risen above the counteracting osmotic pressure of the plasma protein.[10]

3. Effects of Edema of the Lungs on the Respiration and on the Circulation: Clinical experience indicates that when acute pulmonary edema develops in a patient with cardiac asthma the situation becomes extremely serious and may go on to a fatal issue unless proper therapeutic measures are immediately instituted. The reasons for this

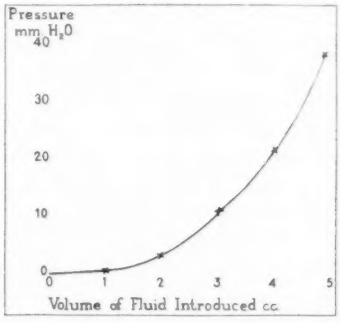

Fig. 8.—This curve illustrates the relations of volume to pressure in a strip of vena cava of a dog. The tributary branches having been ligated, a small cannula was introduced at one end of the vein, and the other end was then ligated. Water was now introduced, 1 cc. at a time, and the pressure was observed. It is seen that the pressure increased very little at first and then rapidly. This result, which is similar to those found by other investigators, is dependent on the fact that the vein is collapsible and easily distensible until it is fairly well filled, but after this point is reached the walls are resistant, and hence any further increase in volume is accompanied by a disproportionately large increment in pressure.

are not far to seek. In the first place, the mere presence of a large amount of fluid in the lower respiratory tract tends to cause violent coughing, and we have shown that cough is a potent cause of dyspnea in

10. The observations which have just been mentioned may afford an explanation of the fact that patients with severe Cheyne-Stokes respiration, although having severe pulmonary congestion, are not likely to have attacks of acute pulmonary edema. Their lungs might become more congested during hyperpnea, but the engorgement would be likely to diminish during apnea, and this would probably tend to prevent the congestion from progressing to the point of producing sudden and severe edema of the lungs.

patients with cardiac failure. Furthermore, in experiments on dogs it was shown [11] that the introduction of fluid into the lungs via the trachea caused marked acceleration of breathing, even though the cough had been abolished by anesthesia. When small amounts of fluid were used, the augmented breathing was evidently a reflex effect, as the respirations were not accelerated if the vagus nerves had been cut previously. When larger amounts of fluid were introduced, there was the additional factor of respiratory stimulation dependent on inadequate aeration of the blood with anoxemia and, in some instances, retention of carbon dioxide. Unless it is assumed that the respiratory physiology of man is radically different from that of the dog, it seems likely that pulmonary edema in man causes stimulation (both reflex and chemical) of the breathing, with a resultant increase in venous inflow, which would tend to cause more congestion and edema and thus to intensify the vicious cycle.

There is another important effect of pulmonary edema, quite aside from its direct influence on respiratory movements. That edema of the lungs may cause severe lack of oxygen in the arterial blood is well known (Eppinger, von Papp and Schwarz; Fraser; subject W. L., table 1 of this paper). It was shown by Harrison and Blalock [12] that arterial anoxemia produced by rebreathing caused marked increase in the cardiac output of dogs. Grollman [13] has recently confirmed their observations by finding that the cardiac output of human subjects was greater at Pike's Peak than at lower altitudes.

Jones [14] studied in this laboratory the effect of "pulmonary edema" (caused by introducing saline solution into the trachea) on the cardiac output of dogs. A summary of his findings is shown in table 3, and it can be seen that of the ten animals studied, eight had an increase in cardiac output after receiving saline solution intratracheally. The degree of increase varied markedly, however, in the different dogs. In one animal no change was noted, and the tenth dog had a diminished cardiac output. The cause of these atypical results in two experiments is still under investigation.

Cause of the Occurrence of Asthmatic Râles in Persons with Cardiac Asthma.—It is well known that in some patients musical and sonorous râles develop during severe attacks of cardiac asthma and more especially if there is an associated acute pulmonary edema. These

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11. Harrison, T. R.; Calhoun, J. A.; Cullen, G. R.; Wilkins, W. E., and Pilcher, C.: Studies in Congestive Heart Failure: Reflex Versus Chemical Factors in Production of Rapid Breathing, J. Clin. Investigation **11**:133 (Jan.) 1932.

12. Harrison, T. R., and Blalock, A.: Regulation of Circulation; Effects of Severe Anoxemia of Short Duration on Cardiac Output of Morphinized Dogs and Trained Unnarcotized Dogs, Am. Physiol. **80**:169 (March) 1927.

13. Grollman, 9.: Physiological Variations of Cardiac Output of Man, Am. J. Physiol. **93**:19 (May) 1930.

14. Jones, E.: Personal communication to the authors.

auscultatory phenomena may be so like those of bronchial asthma as to lead to a mistake in diagnosis if the patient is hurriedly examined. No satisfactory explanation has, to our knowledge, yet been advanced as to the pathogenesis of these physical signs in patients with cardiac asthma. Since attacks of bronchial asthma are usually assumed to be due to active bronchoconstriction, it occurred to us that possibly fluid in the alveoli might have a reflex bronchomotor action. In order to test this hypothesis, experiments were performed on dogs, but we were unable to demonstrate any such effect. (Such negative results are necessarily inconclusive and may have been due to the fact that the method used was not sufficiently delicate to detect small changes in bronchial caliber). Acute edema of the bronchial walls was thought of as another

TABLE 3.—*Effect of Introducing Fluid into the Trachea on the Cardiac Output of Dogs*

		Control Studies		Results After Introducing Saline Solution into the Trachea	
Date	Experiment	Arterial Oxygen Saturation, per Cent*	Cardiac Output per Minute, Liters	Arterial Oxygen Saturation, per Cent	Cardiac Output per Minute, Liters
12/ 6	1	91	1.17	47	3.13
12/13	2	91	2.84	67	2.85
12/17	3	99	2.83	75	3.23
12/20	4	90	1.77	57	2.23
3/11	5	84	2.49	54	3.20
3/18	6	95	0.68	69	1.60
4/ 2	7	86	1.40	78	1.74
4/ 9	8	93	1.34	83	1.57
4/17	9	95	1.51	46	1.13
4/19	10	85	2.86	28	8.27 (?)

* The low arterial saturation present during the control studies is to be attributed to the morphine which was given to the animals in order to keep them quiet during the observations.

possible cause of the auscultatory phenomena under discussion. In order to determine whether or not this occurred, a study was made of pathologic material already at hand.

The lungs from twenty-seven patients were studied. Of these, ten died with cardiac failure; the remaining seventeen were chosen at random. Notes were made in relation to the occurrence of pulmonary edema, bronchial edema, active congestion, passive congestion, pneumonia and miscellaneous complicating factors.

The diagnosis of bronchial edema was made when precipitated material was observed beneath the elevated mucosa. It was realized that elevation or desquamation of the mucosa could occur as an artefact of sectioning or fixation, and therefore the diagnosis of bronchial edema was not made unless this change was accompanied by precipitation of serum beneath the mucosa.

From these cases it seems that we have to differentiate two types of edema, the one associated with a noninflammatory edema of the lungs, the other associated with an acute inflammatory process of the

lungs and bronchi. In the former the wall of the bronchus is entirely free from inflammatory exudate; in the latter it is heavily infiltrated with polymorphonuclear leukocytes.

These two types of edema are illustrated by the photographs in figure 9. The upper photograph illustrates the type of edema which is associated with the acute inflammatory process within and around

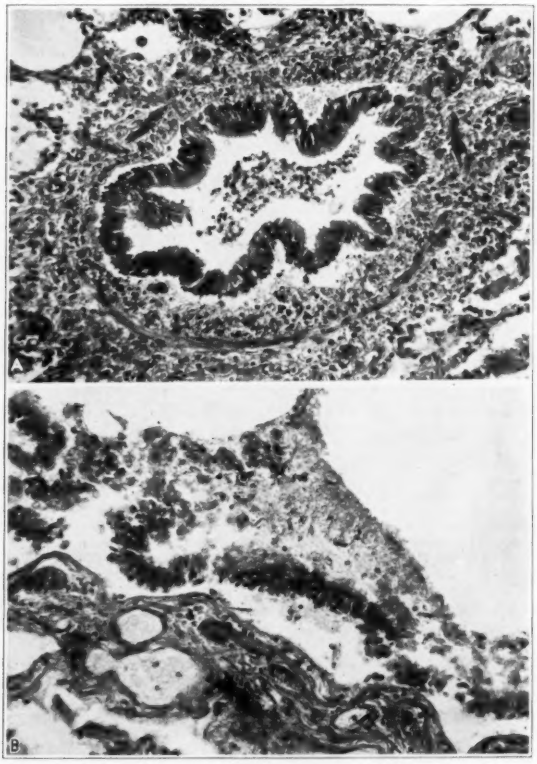

Fig. 9.—Types of bronchial edema. *A*, with acute inflammatory process; *B*, without inflammatory exudate.

the bronchi. The wall is infiltrated with lymphocytes and polymorphonuclear leukocytes, and the fibers are stretched apart. The mucosa is elevated, and there is a collection of precipitated serum beneath it. In the lower photograph the picture is entirely different. The bronchial wall is thin and free from inflammatory exudate. The surrounding alveoli contain precipitated serum but no leukocytes. The mucosa is elevated, and beneath it there is precipitated serum. The desquamation of the epithelium is interpreted as an artefact.

COMMENT

The data which have been reported tend to support the hypothesis that the fundamental underlying cause of cardiac asthma is congestion of the lungs dependent on "back pressure" from dilatation of the left side of the heart. The mechanism is thus quite different from the attacks of coughing and dyspnea experienced by patients with cardiac failure secondary to chronic pulmonary disease (cor pulmonale). The

TABLE 4.—*Various Types of Nocturnal Dyspnea*

Condition	Characteristic Clinical Features	Underlying Cause	Precipitating Causes	Comment
Orthopnea	Dyspnea partially or entirely relieved by sitting up		Assumption of recumbent posture, causing further congestion of lungs	May occur alone; nearly always present in patients with other types of nocturnal dyspnea
Evening dyspnea	Not paroxysmal; absent or mild on first awakening in the morning; develops gradually during the day; worse in the evening; may prevent patient from going to sleep; does not occur during sleep	Dilatation of left side of heart (from overwork or disease) leading to back pressure and congestion of lungs with consequent decrease in respiratory reserve because of (a) decreased vital capacity and (b) reflex stimulation of respiration	Increased degree of pulmonary congestion in evening as compared to morning, because of greater bodily activity when awake than when asleep	Patients may also have cardiac asthma or Cheyne-Stokes respiration
Cheyne-Stokes respiration	Repeated short paroxysms of dyspnea (hyperpnea) separated by intervals free from dyspnea (apnea), appearing only or in exaggerated form at onset of sleep		Sudden decrease in sensitivity of respiratory center at onset of sleep, causing apnea; increased sensitivity of respiratory center on awakening, causing hyperpnea and dyspnea	Other types of nocturnal dyspnea may also be present
Cardiac asthma	Paroxysms of dyspnea occurring after patient has been asleep for some time; often associated with "asthmatic râles"; likely to lead to acute pulmonary edema		Most frequently, cough; also nightmares, desire for urination, abdominal distention, constipation, hunger, warmth, etc.; on awakening, sudden increase in sensitivity of respiratory center leads to increased respiratory movements which cause additional congestion of lungs	Other types of nocturnal dyspnea may also be present

dyspnea in such patients is primarily of pulmonary origin. Because the primary strain is on the right rather than on the left ventricle congestion and edema of the lungs do not occur.

When the observations in the present article are considered in relation to those in the three preceding ones it is possible to make a classification of the various types of nocturnal dyspnea. Such a classification is shown in table 4. It can be seen that nocturnal dyspnea may be of gradual onset (evening dyspnea) or paroxysmal. It may occur either before (evening dyspnea), during (Cheyne-Stokes respiration) or after (cardiac asthma) the onset of sleep. Regardless of the type of dyspnea, the factor of posture is nearly always an important one, and orthopnea

is nearly always present as an additional type of dyspnea. Furthermore, patients with either cardiac asthma or Cheyne-Stokes respiration frequently have evening dyspnea. And finally, all four types of nocturnal dyspnea may occur in the same patient during the same attack of congestive heart failure.

In this series of articles we have emphasized the importance of nocturnal dyspnea. However, the observations are equally applicable to resting dyspnea in general in patients with cardiac disease. A patient who has sufficiently severe pulmonary congestion may parodoxically have any of the various types of nocturnal dyspnea during the day and while awake. In such instances the underlying cause is so severe that the various precipitating factors which have been discussed are unnecessary. Even then, however, the precipitating factors still play a rôle, for no matter how severe the discomfort may be in the morning on awakening, it will usually be worse after the patient has been awake for a number of hours, and unless prevented by proper therapeutic measures paroxysmal exacerbations of the dyspnea will usually occur during or after the onset of sleep. The final result in untreated patients is the agonizing continuous dyspnea which is severe at all times and still worse at some times, which renders sleeping impossible and eating impracticable, which exhausts the patient and produces cardiac cachexia, and which persists until an infarction, a final attack of pulmonary edema or a merciful bronchopneumonia ends the story.

SUMMARY

1. Cardiac asthma has been defined and has been differentiated from other types of paroxysmal and of nocturnal dyspnea occurring in patients with cardiac disease.

2. The dyspnea of cardiac asthma is not usually associated with abnormalities in the oxygen, carbon dioxide or hydrogen ion content of the arterial blood.

3. Relief of the seizure by morphine is not associated with constant alteration in the gases of the blood, but is followed by a decrease in ventilation and is usually accompanied by an increase in vital capacity.

4. Pulmonary congestion, with its twofold effect of decrease in vital capacity and reflex respiratory stimulation, is always present and appears to be the underlying cause of cardiac asthma.

5. There are a number of different precipitating causes of the seizures. Of these, cough is the most common. Less frequently, fear —produced by unpleasant dreams—abdominal distention or warmth may precipitate the seizures.

6. Each of these precipitating factors appears to act by increasing the ventilation.

7. It has been shown that, both in normal persons and in patients with cardiac disease, an increase in ventilation is accompanied by a rise in consumption of oxygen, which occurs immediately and thereby indicates that the cardiac output is also increased.

8. The effects of voluntary overventilation on the vital capacity were studied in normal subjects and in patients with left ventricular failure. The former persons usually had a slight rise in vital capacity, but the reverse effect was usually obtained in the patients.

9. A typical seizure of cardiac asthma was produced in one patient by voluntary overventilation and in another subject by voluntary coughing.

10. Acute pulmonary edema causes both chemical and reflex stimulation of breathing and may thus accentuate dyspnea. It has also been shown that in dogs "edema" of the lungs produced by introducing Ringer's solution may cause marked anoxemia with a consequent increase in the cardiac output.

11. It has been shown that patients dying with congestion of the lungs may have a noninflammatory edema of the bronchial walls, and this is believed to be responsible for the musical and sonorous râles which are often heard during the dyspneic seizures. Thus, an "obstructive" dyspnea may be superimposed on a "reflex" dyspnea.

12. The occurrence of the attacks during sleep appears to be dependent on the depressed irritability which allows the various stimuli mentioned to become excessive before they awaken the patient. On awakening there is marked increase in breathing because of the sudden increase in irritability of the respiratory center, plus the strong stimulus. The resulting increase in ventilation tends to cause additional pulmonary congestion, which leads to further increase in ventilation. The vicious cycle so started may progress to acute pulmonary edema unless it is broken by the patient's assuming the upright posture, by the administration of morphine or by removal of the precipitating cause, i. e., expectoration of mucus, relief from fear of nightmares, etc.

13. The same factors which cause cardiac asthma by night may cause seizures during the day and result in more or less continuous dyspnea.

14. Four types of nocturnal dyspnea occur in patients with cardiac disease; these are orthopnea, evening dyspnea, Cheyne-Stokes respiration and cardiac asthma. They all have a common underlying cause, namely, pulmonary congestion consequent to "back pressure" from the left side of the heart.

Dr. James Dawson, of the Department of Pathology, Vanderbilt University, assisted in the interpretation of changes observed in the bronchial mucosa, and Dr. Edgar Jones permitted us to publish his data concerning the effect of edema of the lungs on the cardiac output.

PERIOSTEAL OSSIFICATION IN MYELOGENOUS LEUKEMIA

REPORT OF A CASE ASSOCIATED WITH ACUTE RHEUMATIC FEVER

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The occurrence of pain in the joints and bones in the course of leukemia, of both the lymphatic and the myeloid type, has been recognized by clinicians for many years (Naegeli,[1] Poynton and his co-workers[2] and Smith[3]). These manifestations have consisted of not only pain and tenderness in the long bones, but also swelling, tenderness and redness in the joints clinically indistinguishable from that which occurs in acute rheumatic fever. These findings usually receive their correct interpretation on the basis of the existence of the hematologic and physical features of leukemia, and little diagnostic difficulty is encountered. Several cases in the aleukemic and acute states, in which the existence of leukemia was less obvious because of the absence of changes in the circulating blood and clinically demonstrable involvement of the liver, spleen and lymph nodes, have presented diagnostic problems in which, particularly, the differentiation from acute rheumatic fever was difficult (Taylor,[4] Karelitz,[5] Seward,[6] Poynton and his co-workers[2] Smith[3] and Cooke[7]).

From the Department of Laboratories and Pediatric Service, Lebanon Hospital.

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2. Poynton, F. J., and Lightwood, R.: Lymphatic Leukemia with Infiltration of the Periosteum Simulating Acute Rheumatism, Lancet **1**:1192 (June 4) 1932. Poynton, F. J., and Moncrieff, A.: Subcutaneous Nodules in the Scalp in Fatal Cases of Glandular Enlargement with Mononucleosis, ibid. **2**:812 (Oct. 19) 1929. Poynton, F. J.; Thursfield, H., and Paterson, D.: The Severe Blood Diseases of Childhood, Brit. J. Child. Dis. **19**:128, 1922.

3. Smith, C. H.: Leukopenic Myeloid Leukemia Associated with Arthritis, Am. J. Dis. Child. **45**:123 (Jan.) 1933.

4. Taylor, H. K.: Periosteal Changes in Lymphatic Leukemia, Radiology **6**:523, 1926.

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6. Seward, B. P.: Lymphatic Leukemia with Severe Pains in the Joints, M. J. & Rec. **131**:444 (May 7) 1930.

7. Cooke, J. V.: Acute Leukemia in Children, J. A. M. A. **101**:432 (Aug. 5) 1933.

Several reported cases contain descriptions of morphologic changes responsible for the skeletal symptoms, but the postmortem examination in many other cases revealed no underlying anatomic basis. The reported anatomic changes, in most instances, refer to osteoporotic and osteosclerotic alterations in the long bones, and, in a few cases, to subperiosteal infiltrations (see Comment).

We have been unable to find a comprehensive description of the exact character of the periosteal changes, which they appear to merit because of their not infrequent discovery in roentgen studies (Geschickter and Copeland [8]). It would appear at first that an infiltration of this type, like, indeed, any other infiltration in the course of leukemia, is of no unusual interest. But the fact that leukemia is not usually considered in the differential diagnosis of periosteal elevation, and that this may exist in aleukemic and acute phases, in which the diagnosis of leukemia is otherwise impossible, merits some focus of attention on this phenomenon.

Our case affords an excellent opportunity for this, as well as for recording a unique instance in which postmortem examination demonstrated the actual coexistence of acute myeloid leukemia and acute rheumatic fever, no similar case having been found in the literature.

REPORT OF CASE

History.—S. A., a girl, white, aged 11½, was first admitted to Lebanon Hospital on Aug. 24, 1932, to the surgical service of Dr. L. M. Kahn. In the past, the patient had had two or three attacks of tonsillitis and had been subject to occasional colds and sore throats. A mastoidectomy had been performed at the age of 16 months. The onset of the menses occurred at the age of 10½, and the patient menstruated regularly every twenty-eight days, for six days. The bleeding was never excessive. The last period occurred in August, and the patient had an amenorrhea until the time of death in November.

On admission, she complained of having had attacks of pain in the lower half of the left arm since June, 1932. On examination a definite fusiform swelling of the lower half of the left humerus, with tenderness on pressure, was found. The temperature ranged between 98.6 and 100.5 F. Examination of the blood showed the following: hemoglobin, 80 per cent; red cells, 4,000,000; white cells, 16,400; polymorphonuclears, 82 per cent, and lymphocytes, 18 per cent. The picture was essentially that of an infection, and a tentative clinical diagnosis of subacute osteomyelitis was entertained. However, roentgen examination of the left elbow disclosed a marked thickening of the periosteum on all sides of the left humerus in its lower half. The cortex and medulla showed no abnormality (fig. 1). The Wassermann reaction was negative, and the Wassermann examination of the parents' blood done several months later was also negative. A diagnosis of chronic

8. Geschickter, C. F., and Copeland, M. M.: Tumors of Bone, New York, American Journal of Cancer, 1931, p. 617.

periostitis of unknown origin was made, and the patient was discharged on September 1, one week after admission, unimproved.

After returning home the patient continued to complain of pain in the left elbow, and in the right ankle and knee as well. About two weeks after her discharge tonsillectomy was performed, five carious teeth being extracted at the same time. These procedures were not followed by any unusual degree of hemorrhage. The patient was apparently well for the next week; then she began to complain of pain in the right wrist, and then in the left wrist and in the toes of both feet. The

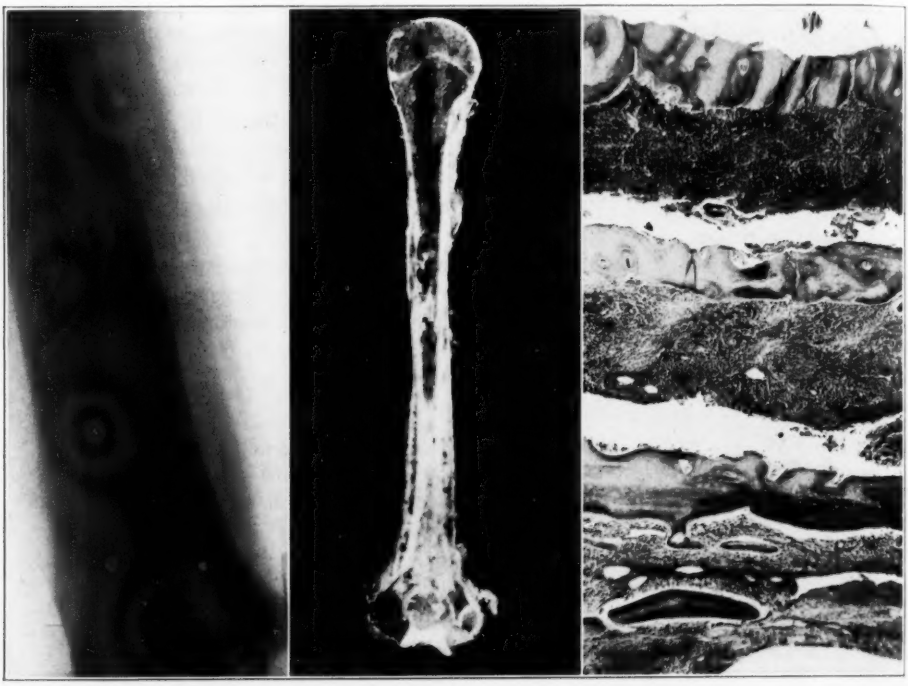

Fig. 1.—The roentgenogram on the left, taken on Aug. 25, 1932, shows periosteal elevation and thickening at the lower end of the left humerus. The center photograph is a cross-section of the left humerus and shows periosteal elevation and thickening and subperiosteal infiltration. The marrow is leukemic. The photomicrograph on the right shows the histologic appearance of the elevated, thickened periosteum at the lower end of the left humerus. The shaft of bone is below, out of the picture. Newly formed bony lamellae with intervening layers of leukemic infiltrate are seen.

temperature rose and became septic, and a week after the onset of these symptoms, on October 6, the patient was readmitted to the pediatric service of Dr. Charles Herrman.

Examination and Course.—On examination, the child appeared acutely ill. There were slight swelling, tenderness and limitation of motion of the left wrist. The

left elbow showed the same findings as on previous examination, but there was no tenderness. The small joints of the fingers and toes were tender but not swollen. The heart showed no abnormalities, except for tachycardia. The liver, spleen and lymph nodes were not palpable. There was also a purplish, more or less generalized, scarlatiniform erythema, especially marked on the abdomen and chest. This was considered by Dr. L. Chargin, the attending dermatologist, to be due to the administration of salicylates, and later when amidopyrin was substituted, the rash disappeared. The temperature on admission was 102 F., and the pulse rate, 130. The blood count showed the following: hemoglobin, 55 per cent; red cells, 3,610,000; white cells, 20,000; polymorphonuclears, 72 per cent; lymphocytes, 26 per cent, and monocytes, 2 per cent. The administration of salicylates and amidopyrin produced a marked remission in fever and pain in the joints.

Data on Blood Studies

	8/24	10/6	10/18	10/29	11/5	11/11	11/16
Hemoglobin.....	80%	56%	52%	51%	46%	35%	28%
Red blood cells.....	4,000,000	3,610,000	3,520,000	3,610,000	2,910,000	1,920,000	1,760,000
White blood cells...	16,400	20,000	37,200	56,800	89,200	163,000	184,000
Neutrophils.....	82%	72%	78%	73%	30%	20%	15%
Lymphocytes.....	18%	26%	17%	17%	26%	8%	7%
Monocytes.....	....	2%	3%	1%	3%	1%	...
Eosinophils.....	....	...	2%	1%	...	...	...
Myelocytes							
Neutrophilic.....	....	...	...	...	6%	46%	20%
Eosinophilic.....	....	...	...	4%	27%	....	....
Myeloblasts.....	....	...	...	3%	8%	24%	58%
Normoblasts.....	....	...	...	1%	...	1%	....
Platelet count.....	....	...	...	120,000	...	70,000	....
Reticulocytes.....	....	...	...	3%	...	1%	....
Bleeding time.....	....	...	...	...	4 min.	...	....
Coagulation time..	....	...	...	...	5½ min.	...	....

On October 11, five weeks prior to death, the blood count was essentially the same as previously, the leukocytes numbering 18,300. Examination of the heart showed no clinical evidence of involvement, but two weeks later a systolic murmur was heard over the fourth intercostal space to the left of the sternum, and the second aortic sound was accentuated. An electrocardiographic tracing revealed myocardial damage, as evidenced by slurring of the QRS complex in all leads, and two premature auricular contractions in lead I. There was also absence of sinus arryhthmia, but no increase in the PR interval.

On October 18, four weeks prior to death, a routine blood count gave the first evidence of irregularity in the blood picture. The leukocytes numbered 37,200; the differential count was not significantly changed. The temperature at this time was normal.

On October 22, three weeks before death, the liver was first felt two finger-breadths below the costal margin. On October 24, the spleen was palpated for the first time just under the costal margin, and small lymph nodes were felt in the neck, axillae and groins. On October 25, after a tourniquet was applied to the arm in order to obtain a specimen of blood, it was noticed that many petechial hemorrhagic spots developed below the site of the tourniquet.

From this time on, progressive increase in size of the palpable lymph glands and spleen could be followed. The glands became moderately enlarged; the liver grew daily in size, and after two weeks extended to the umbilicus; at death, it almost filled the abdomen. The spleen did not appear to grow as rapidly, but roentgen examination showed it to be considerably enlarged.

On November 7, a few petechial hemorrhages were noticed on the face. These rapidly became more numerous and widespread, involving mostly the face, palate, chest and abdomen. Many hemorrhages were seen in the ocular fundi. One of these with a pale center was considered typical of leukemia by Dr. J. Ziporkes, the attending ophthalmologist.

Repeated examinations of the blood showed an advancing anemia and a progressive increase in the number of leukocytes with a differential count indicative of the presence of a myelogenous leukemia (Dr. H. Frosch, hematologist). At the time of death, the leukocyte count was 184,000. The cells were mainly of the myeloid series. At the beginning, immature polymorphonuclear cells predominated, with occasional myeloblasts and myelocytes. There was a gradual increase in the number of myeloblasts, which rose from 3 per cent, until at the time of death they constituted 58 per cent of the total number of cells. The platelet count was 120,000 per cubic millimeter; the reticulocytes, 3 per cent. Bleeding and coagulation time were within normal limits. The blood chemistry was normal. Repeated cultures of the blood were sterile.

Roentgenographic examination of the bones revealed a moderate degree of decalcification of all the bones of the upper extremities; small areas of bone absorption along the outer aspects of both scaphoid bones and in the lower end of the shaft of the left ulna, and periosteal thickening along the left humerus, as observed previously, and in the right ulna as well.

On November 11, a biopsy of a right inguinal lymph node was performed and was reported as showing "marked extramedullary myelopoiesis as seen in leukemic myelosis."

On November 12, 250 cc. of citrated blood was given by transfusion. Following the transfusion, the patient became much worse. She was drowsy and irritable, uttered loud cries and appeared to be very sensitive to touch. She became dyspneic, and complained of abdominal pain and inability to breathe, and died on November 16, six weeks after the second admission and five months after the onset of the symptoms.

Biopsy.—The capsule of the inguinal lymph node was thin, and for the most part, not infiltrated. A few foci of infiltration, however, were seen in the pericapsular fat tissue. The original lymphatic structure was recognizable in a few areas. The remainder of the node consisted of a diffuse arrangement of pale, large, young cells. With the oil immersion lens, the finer details of these cells appeared as follows: Scattered, isolated cells and solid nests of cells corresponded to the most primitive, undifferentiated, mesenchymal type. They were large and stellate, with processes. The cytoplasm did not stain. The nucleus was oval and free from nucleoli. A later stage of differentiation was seen in cells which were partially rounded. They possessed a basophilic cytoplasm, sometimes heavily granulated, a darker nuclear membrane, and one or two large, usually dark-staining nucleoli. A still later stage was recognized in completely rounded cells, somewhat smaller than the previously described type. These contained cytoplasmic granules, frequently eosinophilic, and a single round nucleus, possessing a sharp membrane and

multiple dark nucleoli. Many mitoses were encountered, as well as some mature polymorphonuclear cells. The blood vessels and lymphatics contained numerous immature granulocytes. An occasional plasma cell was seen (fig. 2).

The diagnosis was "marked extramedullary myelopoiesis as seen in leukemic myelosis."

Autopsy.—Gross changes: The gross appearance is shown in figure 3.

There was no jaundice, but there was a slight pitting edema over the anterior tibial regions, and numerous petechial hemorrhagic flecks were seen over the face, neck and arms. Similar flecks were seen in the conjunctivae and mucous membranes of the mouth. There was a scar in the right inguinal region where a biopsy specimen had been obtained previously. No rheumatic subcutaneous nodules were found.

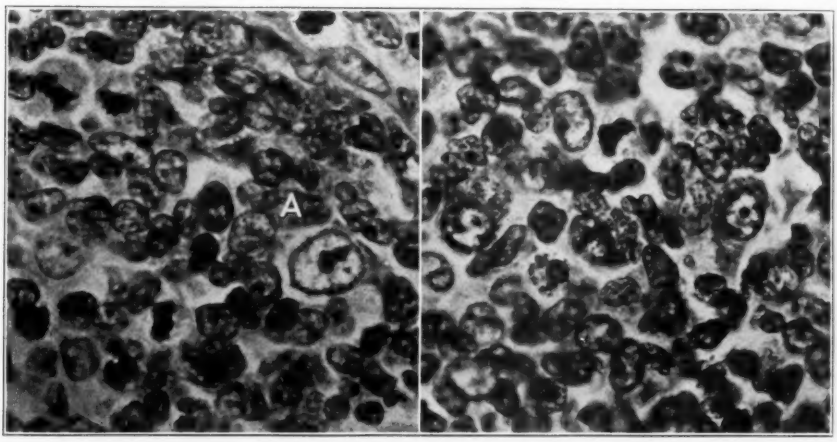

Fig. 2.—Photomicrographs of lymph node secured for biopsy. On the left is shown diffuse reticulum cell proliferation, with numerous mitoses. *A* indicates early differentiation into hemocytoblast. On the right are shown granules in cytoplasm of fixed mesenchymal cells undergoing hemocytoblastic differentiation.

The liver extended to the iliac crest on the right side and diagonally across the umbilicus to the hilus of the spleen. Hemorrhagic flecks were seen in the mesentery and serosal surfaces of the bowel.

All the lobes of the lungs had a distinctly nodular, firm consistency. A few scattered pleural petechiae were noted. On section, the lung, which cut with increased resistance, presented diffuse, confluent, raised, dry, granular hemorrhagic areas. The trachea and bronchi contained some purulent exudate, and their mucous membrane was markedly congested.

The pericardial cavity did not contain an increased quantity of fluid or adhesions. All four chambers of the heart were moderately dilated, but there was no distinct hypertrophy. The epicardium and endocardium contained scattered small hemorrhagic flecks. The foramen ovale was closed. The tricuspid, pulmonic and aortic valves presented no abnormalities. The cusps of the mitral valve were diffusely thickened, and, along the entire closing margin, a row of small, firm, pale vegeta-

Fig. 3.—Gross appearance of organs at autopsy: *A*, the lungs showing confluent bronchopneumonia; *B*, the kidneys showing diffuse pallor and focal hemorrhagic infiltrations; *C*, the esophagus showing hemorrhagic leukemic plaques and shallow ulcers, with petechial hemorrhages of the gastric mucosa; *D*, the liver showing diffuse periportal infiltrations, and *E*, the spleen showing diffuse infiltrations and infarcts.

tions was present. The blood vessels were not grossly visible in these cusps. The chordae tendineae were not thickened or adherent, and their insertion was normal. The left auricular endocardium was smooth. The coronary arteries were normal. The aorta was of normal caliber and elasticity. The myocardium was reddish brown, and presented scattered hemorrhagic and grayish streaks.

The thymus appeared hyperplastic.

The liver weighed 2,500 Gm. The capsule was a grayish yellow and pale, and the parenchyma shining through had a cobbled appearance. On section, the surface consisted of an anastomosing network of broad gray-white channels. No nodular infiltrations were seen. The gallbladder and bile ducts were normal.

The peripancreatic lymph nodes were enlarged, and at one point there appeared to be a nodular infiltration of the pancreas.

The spleen weighed 400 Gm. It was fairly firm in consistency. The capsule was thickened, and the organ was a pale, reddish gray. Three small anemic infarctions, with surrounding hemorrhagic zones, were present. The parenchyma was a pale, reddish gray and had a soft consistency. The pulp could be scraped easily, and the details of the follicles were hard to discern.

The suprarenals were normal.

The capsules of the kidneys could be stripped easily. The color was exceedingly pale buff, and there were numerous scattered small and large hemorrhages, some of which were raised and nodular and had white centers. On section, the cortex was of normal width, and the corticomedullary zone was markedly congested. Several of the surface hemorrhages extended in wedge form toward the medulla. The pelves and ureters were normal. The bladder presented several submucosal hemorrhages in the region of the trigon.

The uterus was infantile. The adnexae were normal.

The esophagus near the cardiac portion of the stomach presented two shallow ulcers about 5 mm. in diameter, and also two raised hemorrhagic, dry, granular plaques. The mucosa of the stomach in the cardiac region was flecked with petechial hemorrhages. The lymphatic tissue showed nodular hyperplasia, giving the mucosa a cobble-stone appearance. Peyer's patches and the solitary follicles throughout the gastro-intestinal tract were hypertrophied. The submucosal lymphatic tissue of the appendix appeared diffusely hyperplastic.

Transection of the left humerus revealed a soft, grayish-red, cellular marrow in the epiphysis as well as in the shaft. From the midportion to the epitrochlear condyles, the periosteum was lifted and reduplicated into three or four calcified layers, between which a tissue corresponding in appearance to the marrow was present. The rib marrow was soft, increased in quantity and grayish red. Cross-section of a vertebra and of the sternum revealed beefy-red, soft marrow.

Enlarged lymph nodes were found in the supraclavicular, axillary, inguinal, cervical, mediastinal, mesenteric, retroperitoneal, omental, perigastric, peripancreatic and hepatic and splenic hilar regions. The appearance of these glands was quite uniform. They were globular, discrete, freely movable in their surrounding tissue and soft. The capsule was thin, and on section retracted readily. The cut surface was grayish yellow, and in some of the nodes hemorrhagic areas could be seen. The appearance was homogeneous, and no follicular structure or fibrous areas could be discerned.

Histologic Examination.—At the closing margin of the posterior mitral leaflet, there was a thrombotic verrucous lesion with early organization in the form of palisades of young connective tissue cells. The left auricular endocardium was edematous, but no MacCallum lesion was present. There were leukemic infiltra-

ing diffuse pallor and focal hemorrhagic infiltrations; *C*, the esophagus showing hemorrhagic leukemic plaques and shallow ulcers, with petechial hemorrhages of the gastric mucosa; *D*, the liver showing diffuse periportal infiltrations, and *E*, the spleen showing diffuse infiltrations and infarcts.

tions in the pericardium. The apex of the ventricular myocardium showed some interstitial scarring. All vessels were engorged with leukemic blood cells, and several hemorrhagic, leukemic infiltrations were seen. Many young Aschoff bodies and a few perivascular scars were present (fig. 4).

In the lungs were confluent pneumonic areas. The alveolar exudate consisted of polymorphonuclear cells and fibrin, despite the engorgement of the local capillaries with leukemic cells. Many of the alveolar walls were necrotic. Bronchi contained purulent exudate. No Aschoff bodies were seen.

Periportal fields showed broad anastomosing channels of leukemic infiltration which pervaded the entire section. The sinusoids were distended with leukemic blood cells. The Kupffer cells did not show any increase in number or changes in form. The capsule was thin and diffusely infiltrated. There were several areas of atrophy of the central cords of the liver with marked fatty change.

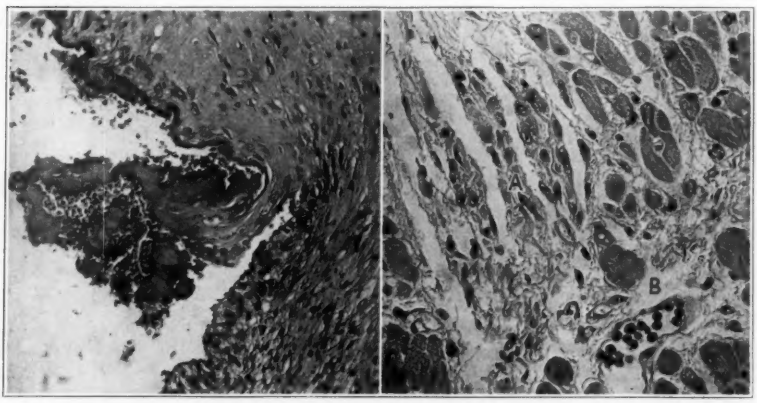

Fig. 4.—Photomicrographs showing histologic changes in the heart. On the left is a section of the posterior mitral leaflet showing verruca with superficial thrombotic mass and palisading of young connective tissue cells. On the right is a section of the myocardium showing large, young Aschoff body (*A*), and blood vessel containing leukemic cells (*B*).

Within the follicles of the spleen, central depletion was seen with some hyalinization of the capillary walls and pyknotic nuclear changes. The lymphatic tissue of the follicles consisted almost exclusively of small lymphocytes. Immature granulocytes were not present, and there was a sharp differentiation between lymphatic tissue of the follicle and the extensive leukemic infiltration of the pulp. The pulp was extremely cellular, the cells consisting of lymphatic cells and granulocytes in various stages of maturity. The sinuses could be made out distinctly in areas, and the endothelium of the sinus did not show any significant alteration. Several of the splenic veins in the trabeculae showed subintimal infiltration.

Diffuse infiltrations, which surrounded individual glomeruli and tubules, were present in the cortex of the kidney. Some of these infiltrations assumed a nodular form. There was also a wedge-shaped area of necrosis, at the apex of which a thrombosed vein was present. Infiltrations were also present around the arcuate

arteries and in scattered areas in the medulla. Glomerular capillaries were frequently seen to contain leukemic blood cells.

Portions of the pancreas were so extensively infiltrated by leukemic cells that the parenchyma was completely obliterated. In other areas, the acini were separated by broad zones of infiltrate. The ducts and vessels were normal. The islets showed no significant change.

The sinusoids of the suprarenals contained leukemic blood.

The parenchyma of the thymus appeared markedly hyperplastic, and normal corticomedullary zones were no longer recognizable. Evidence of extramedullary myelopoiesis could be found in the cellular constituents.

The mucosal lymphatic tissue of the appendix had lost its normal follicular character, and there was a dense infiltration of the mucosa and submucosa by leukemic cells.

Section of a Peyer's patch in the small intestine revealed extensive hypertrophy and the presence of many myeloid cell types.

The spinal cord was normal.

Sections of the small lymph nodes revealed a thin unfiltrated capsule and partially altered structure in which elements of original architecture, such as marginal and medullary sinuses, could still be discerned. There was, however, a uniformity of cell distribution which in nowise suggested the normal distinctions of cortex medulla and secondary follicles. The cell types present revealed a striking loss of the original small lymphatic types, and, while some of these still remained, the predominating forms were those of the granulocytic series; the largest proportion were very immature; many of them were fixed, mesenchymal cells, many corresponded to hemocytoblasts, and numerous eosinophilic and neutrophilic granular derivatives were present. An occasional megakaryocyte was encountered. Frequent mitoses were seen in the free cells. The blood vessels and lymphatics contained leukemic cells.

A longitudinal section of periosteum revealed from five to six flat layers of osseous tissue showing typical bony lamellae and lacunar spaces. Between these were flat layers of leukemic cells compactly arranged, and showing streaming of cells, probably due to pressure. Several bony trabecular connections were seen between the various osseous layers. A cross-section of the shaft of the humerus revealed a marked widening of the haversian and volkmann canals, the lumens containing not only blood vessels, but also large aggregations of leukemic infiltrate. The parallel surface lamellae of the cortical substance were well defined and showed no alteration in the nature of separation or splitting. Examination of longitudinal and cross-sections of the shaft revealed a predominantly longitudinal arrangement of the new bony lamellae. The periosteum was seen outside the most peripheral bony lamellae and between these two, as well as in the striated muscle peripheral to the periosteum, leukemic infiltrate was present.

From a study of these areas and from the irregular arrangement of the reduplicated subperiosteal bony trabeculae, it was possible to determine that these reduplicated layers represented new formation and did not arise by the splitting away of the superficial layers of the cortical lamellae.

Résumé of Case.—The patient, a white girl, aged 11½, was admitted to Lebanon Hospital on Aug. 24, 1932, with a painful, tender swelling of the lower half of the left humerus, which the roentgenogram revealed to be a marked thickening of the periosteum on all sides of the humerus in

its lower half. Examination of the blood revealed a negative Wassermann reaction. The leukocytes numbered 16,400, with a polynucleosis of 82 per cent. No immature forms were observed.

On October 6, following a tonsillectomy and the extraction of five carious teeth, the patient was readmitted to the hospital with a syndrome of fever and migratory polyarthritis. A diagnosis of acute rheumatic fever was made and supported by the response to therapy and the development of cardiac involvement.

The first evidence of a dyscrasia was disclosed by the persistent high leukocyte count in the presence of a normal temperature. The progressive enlargement of the liver, spleen and lymph nodes, the development of the typical blood picture and, finally, biopsy of a lymph gland, which showed diffuse myelopoiesis, established the diagnosis of myeloid leukemia, and the original diagnosis of rheumatic fever was abandoned.

The autopsy, however, revealed the classic pictures of rheumatic fever in the heart and of a generalized acute leukemic myelosis.

The diagnosis from the biopsy was marked extramedullary myelopoiesis as seen in leukemic myelosis.

The anatomic diagnosis was: (1) "acute" generalized leukemic myelosis with involvement of the lymph nodes, liver, spleen and bone marrow; (2) leukemic infiltration in the kidneys, heart, esophagus, pancreas, small intestine and appendix; (3) ossified periosteal reduplications with intervening leukemic infiltrates in the region of the lower part of the left humerus; (4) acute rheumatic verrucous endocarditis of the mitral valve, and acute rheumatic myocarditis; (5) multiple splenic infarctions; (6) ulceration of the esophagus with leukemic infiltrations, and (7) diffuse bilateral, confluent bronchopneumonia.

COMMENT

It was felt impossible to retain the original diagnosis of rheumatic fever when the subsequent appearance of enlarged liver, spleen and lymph nodes, and positive blood findings established the presence of leukemia. The leukemia appeared to account for all the clinical phenomena, including the electrocardiographic evidences of myocardial damage, which were not of a type considered characteristic of rheumatic fever. These changes and the systolic blow which later appeared were held to be consistent with the diagnosis of leukemia on the theoretical basis of a marked anemia and the possibility of myocardial damage coincident with leukemic infiltration and hemorrhage in the myocardium as part of the generalized process. A further theoretical possibility was the development of a terminal thrombo-endocarditis, such as is not infrequently encountered in cases of leukemia, as well as in other wasting diseases.

The course of events suggests that the onset of the acute infection, in this instance rheumatic fever, served to convert the aleukemic into a leukemic phase, and to generalize and accelerate the leukemic process. The rapidity with which this progressed was remarkable. Perceptible increases in size of the lymph nodes, liver and spleen occurred almost daily, and within a period of one month, heretofore impalpable hematopoietic structures underwent such enlargement that the liver reached to the crest of the ileum; the spleen descended three or four finger-breadths below the costal margin as well as upward, and large clusters of lymph nodes were palpable in all their normal habitats.

The observation of progressive enlargement of the lymph nodes while the patient remained in the hospital offered the opportunity of establishing a time factor in connection with the histologic picture. Sections of a lymph node, the enlargement of which was known to have dated back for a period of only two weeks, revealed the earliest stages of extramedullary granulopoiesis. Klemperer,[9] in citing the evidence for the derivation of hemocytoblasts from the cellular reticulum in extramedullary sites in postembryonal life, stated that he has observed in the spleens in two cases of acute myeloid leukemia stages suggestive of transformation of fixed elements into free hemocytoblasts identical with the stages seen in the embryo.

The Aschoff bodies in the myocardium corresponded in all details to the classic forms characteristic of acute rheumatic fever, and their structure corresponded to the earlier stages of the life cycle of the Aschoff body (Gross and Ehrlich,[10] Klinge [11]). The leukemic infiltrations in the heart and the Aschoff nodules coexisted side by side without apparently exerting any mutual effects (fig. 4).

The pneumonic infiltrations consisted exclusively of mature polymorphonuclear cells, despite the predominant "blast" type of cell in the pulmonary vessels and peripheral blood, a characteristic phenomenon in infections occurring in the course of leukemia, recently commented on by Jaffé.[12]

The degree of periosteal changes observed in the first roentgenogram gives unequivocal proof that the leukemia had existed for some time

9. Klemperer, P.: Relationship of the Reticulum to Diseases of the Hematopoietic System, in Contributions to the Medical Sciences in Honor of Dr. Emanuel Libman by His Pupils, Friends and Colleagues, New York, International Press, 1932, vol. 2, p. 655.

10. Gross, L., and Ehrlich, J. C.: Histological Studies on the Aschoff Body, Am. J. Path. **6**:621, 1930.

11. Klinge, F.: Das Gewebsbild des fieberhaften Rheumatismus, Virchows Arch. f. path. Anat. **279**:438, 1930.

12. Jaffé, R. H.: Morphology of the Inflammatory Defense Reactions in Leukemia, Arch. Path. **14**:177 (Aug.) 1932.

before the patient's first admission to the hospital, at which time there were no abnormal cells in the blood smear. The onset of the rheumatic fever can be related to the appearance of generalized manifestations in the joints following her discharge, for which tonsillectomy and dental extractions were performed, and which on roentgen and postmortem examination could not be proved to have occurred on a leukemic basis. Smith [3] and others have described cases of leukemia in which the manifestations in the joints, because of swelling, redness and tenderness, of migratory character, were indistinguishable from those encountered in rheumatic fever. Mention may be made of the disappearance of the fever and symptoms in the joints in our patient after the administration of salicylates and amidopyrin. In Smith's case, at a time when the patient was still considered to be suffering with rheumatic fever, the skeletal symptoms showed no response to therapy with salicylates.

Sections of the elevated periosteal layers at the lower end of the left humerus revealed newly formed osseous tissue between which leukemic infiltrations were present. Examination of the lamellar architecture of the underlying cortex revealed completely intact cortical bone. This finding indicates that the osseous layers outside of the cortex arose by the formation of new bone, and not by the splitting away of cortical lamellae by the pressure of leukemic infiltrate (fig. 1). Secondary changes occurring in the bone in the course of leukemia, both lymphatic and myeloid, have been well recognized for many years. Since the original description of Heuck,[13] in 1879, the majority of anatomic descriptions of alterations in the bone complicating this disease are concerned with osteoporotic and osteosclerotic changes (Mott,[14] Schwarz,[15] von Baumgarten,[16] C. Sternberg [17] and Stephens and Bredeck [18]). However, the occurrence of periosteal elevations and so-called "ossifying periostitis," on the basis of subperiosteal leukemic infiltrations, has been reported in a few rare instances. The cases of Smith, Taylor, Karelitz and Poynton and Lightwood contain roentgen evidences and in some cases references to the postmortem recognition of subperiosteal changes of this type.

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13. Heuck, G.: Zwei Fälle von Leukämie mit eigenthümlichem Blutrespektive Knochenmarksbefund, Virchows Arch. f. path. Anat. **78**:475, 1879.

14. Mott, F. W.: A Case of Spleno-Medullary Leukaemia with Haemorrhage into the Cochlea and Semicircular Canals, Associated with Deafness and Loss of Balance, Med.-Chir. Tr., Lond. **83**:209, 1899-1900.

15. Schwarz, E.: Ein Fall von Leukämie mit Riesenzellenembolie und allgemeiner Osteosklerose, Ztschr. f. Heilk. **22**:294, 1901.

16. von Baumgarten, P.: Myelogene Pseudoleukämie mit Ausgang in allgemeine Osteosklerose, Arb. a. d. Geb. d. path. anat. Inst. zu Tübingen **2**:499, 1899.

17. Sternberg, C.: Leukämie und Osteosklerose, Ergebn. d. allg. Path. u. path. Anat. **9**:419, 1903.

18. Stephens, D. J., and Bredeck, J. F.: Aleukemic Myelosis with Osteosclerosis, Ann. Int. Med. **6**:1087, 1933.

In 1901, von Jaksch [19] described a case of generalized periosteal elevations with ossification, associated with a myelocythemia and an enormous spleen. He considered the periosteal disease primary, and the changes in the blood and splenic enlargement secondary. Schlagenhaufer,[20] in 1904, reported periosteal changes, similar to those which von Jaksch observed, occurring in a patient with a widely metastasizing carcinoma of the pharynx. He felt that in his case, and also in von Jaksch's case, the periosteal changes were not related to the current disease, and suggested that since similar changes had been observed in cases of arsenic poisoning, and since therapeutic doses of arsenic had been given in both his case and in von Jaksch's case, this may have been the etiology of the periosteal change. In 1905, Carl Sternberg, in discussing von Jaksch's case, expressed the view that it was really a leukemia and should be classed with Hueck's and Schwartz' cases as a leukemia with secondary changes in the bone. In 1908, Fabian [21] mentioned the occurrence of periosteal lymphomas in large cell lymphatic leukemia. Similar tumor masses have been repeatedly described in chloroma, but nodular masses of this type are quite distinct from the diffuse, flat infiltrations with which we dealt. The only other reference to this change which we have been able to discover is that of Geschickter and Copeland,[8] who mentioned subperiosteal infiltrations in leukemia and who published a roentgenogram showing this change.

The occurrence of subperiosteal elevations due to leukemic infiltration at a time when there was no enlargement of the liver, spleen or lymph nodes and no immature cells in the circulating blood would indicate that coincident with the rheumatic infection there was not only an invasion of the circulating blood by immature cells, but also a generalization of the hematopoietic activity of the reticulum cells of the various organs, which, until that time, was more or less localized to the periosteal elevation observed by roentgenographic examination and perhaps to other restricted foci in the body. These facts throw some light on the manner of origin and progress of a leukemia and on the nature of so-called "acute leukemia."

The published differential diagnoses of periosteal elevation and periosteal ossification, which include healed fractures, trauma without fracture, osteomyelitis, syphilis, tuberculosis, typhoid, leprosy, pulmonary osteo-arthropathy, osteitis deformans, rickets, scurvy, chronic icterus, arsenic and phosphorus poisoning and tumors of the bone

19. von Jaksch, R.: Multiple Periostaffection und ein myelogene Leukämie mahnender Blutbefund, Ztschr. f. Heilk. **22**:259, 1901.

20. Schlagenhaufer, F.: Ueber diffuse ossifizierende Periostitis, Ztschr. f. Heilk. **25**:364, 1904.

21. Fabian, E.: Ueber Leukämie besonders ihre grosszellige lymphatische Form, Centralbl. f. allg. Path. u. path. Anat. **19**:49, 1908.

(Teleky,[22] Beutenmüller,[23] Obermayer,[24] Giles and M. Sternberg[25]), do not mention leukemia, and it would appear from our experience and a survey of the literature that this disease should be considered when such periosteal changes are observed clinically and by roentgenographic study, even in the absence of positive blood and physical findings.

SUMMARY

1. A case of "acute" myeloid leukemia which presented the clinical picture of acute rheumatic fever during an aleukemic phase, and which at autopsy presented the anatomic evidence of both diseases, is reported.

2. The occurrence of periosteal changes in the left humerus at the beginning of the clinical course was found at autopsy to have occurred on the basis of repeated subperiosteal leukemic infiltrations with secondary ossification in layers.

3. A review of the literature of the changes in the bone in leukemia and study of our case result in the inclusion of leukemia in the differential diagnosis of periosteal elevation and ossification.

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22. Teleky, L.: Beiträge zur Lehre von der Ostéoarthropathie hypertrophiante pneumonique, Wien. klin. Wchnschr. **10**:143, 1897.

23. Beutenmüller, H.: Toxigene Osteoperiostitis ossificans bei chronischem Icterus, Berl. klin. Wchnschr. **45**:1001, 1908.

24. Obermayer, F.: Knochenveränderungen bei chronischem Icterus, Wien. klin. Rundschau **11**:645, 1897.

25. Sternberg, M.: Vegetationsstörungen und Systemerkrankungen der Knochen, in Nothnagel, C. W. H.: Spezielle Pathologie und Therapie, Vienna, Alfred Hölder, 1899, vol. 7, sect. 2, pt. 2, p. 72.

INDEX TO VOLUME 53

Book reviews are grouped together and are indexed under that heading in alphabetical order, under the letter B.

Abramson, J.: Heart in myxedema, 165
Acid-Base Equilibrium in pathologic conditions; serum electrolyte changes in acute mercuric chloride poisoning, 885
studies of blood in normal pregnancy; conductivity, total base, chloride and acid-base equilibrium, 527
Ackerman, W.: Metabolic exercise tolerance test for patients with cardiac disease; feasible method for using excess oxygen consumption and recovery time of exercise as criteria of cardiac status, 710
Adrenals: See Suprarenals
Amino-Acids, muscular dystrophy and atrophy; clinical and biochemical results following oral administration of amino-acids, 435
Anemia, constancy of iron in blood plasma and urine in health and in anemia, 551
pernicious; gastro-intestinal studies; determinations of enzymes on autopsy specimens from cases of pernicious anemia and pellagra, 675
Angina Pectoris, clinical considerations with reference to prognosis, 120
factors involved in production of skeletal muscle pain, 814
Aorta; cardiac output: its related functions in case of coarctation of aorta, 35
Arteriosclerosis, effect of arteriosclerosis and benign and malignant hypertension on area of histamine flares, 865
relation of plasma cholesterol to obesity and to some complicating degenerative diseases (diabetes mellitus, essential hypertension, osteo-arthritis and arteriosclerosis), 423
Arteritis of temporal vessels; previously undescribed form, 400
Arthritis, relationship between anatomic changes in knee joint with advancing age and degenerative arthritis, 325
rheumatoid (atrophic) arthritis; bacteriologic cultures of synovial fluid and of tissues, 87
Asthenia, neurocirculatory, etiology and symptoms of analysis of 100 cases with comments on prognosis and treatment, 633
Asthma, congestive heart failure; observations concerning mechanism of cardiac asthma, 911
Atabrine: See Malaria, therapy
Atrophy, muscular dystrophy and atrophy; clinical and biochemical results following oral administration of amino-acids, 435
Ayman, D.: Heredity in arteriolar (essential) hypertension; clinical study of blood pressure of 1,524 members of 277 families, 792

Bacteremia, Salmonella suipestifer bacteremia with acute endocarditis, 699
Bacteria, Salmonella: See Salmonella
Banks, B. M.: Relapses in chronic ulcerative colitis; causes and prevention, 131
Bargen, J. A.: Relapses in chronic ulcerative colitis; causes and prevention, 131
Barshop, N.: Effect of toxemia on tolerance for dextrose and on action of insulin, 689
Beard, H. H.: Muscular dystrophy and atrophy; clinical and biochemical results following oral administration of amino-acids, 435
Birnbaum, W.: Generalized thrombo-angiitis obliterans; report of case with involvement of retinal vessels and suprarenal infarction, 410
Blair, J. E.: Rheumatoid (atrophic) arthritis; bacteriologic cultures of synovial fluid and of tissues, 87
Blood: acid-base balance in pathologic conditions; serum electrolyte changes in acute mercuric chloride poisoning, 885
cholesterol and hypometabolism; suprarenal and pituitary deficiency, obesity and miscellaneous conditions, 825
cholesterol and thyroid disease; myxedema and hypercholesteremia, 762
cholesterol; relation of plasma cholesterol to obesity and to some complicating degenerative diseases (diabetes mellitus, essential hypertension, osteo-arthritis and arteriosclerosis), 423
constancy of iron in blood plasma and urine in health and in anemia, 551
in normal pregnancy; blood and plasma volumes, 71
in normal pregnancy; conductivity, total base, chloride and acid-base equilibrium, 527
in normal pregnancy; hemoglobin and cell volume coefficients; erythrocyte volume, hemoglobin content and concentration; color, volume and saturation indexes, 345
in normal pregnancy; hemoglobin, hematocrit and erythrocyte determinations and total amount of variations of each, 188
in normal pregnancy; percentages and grams per kilogram of serum protein and fibrin and variations in total amount of each, 353
in normal pregnancy; plasma cholesterol in milligrams per hundred cubic centimeters, grams per kilogram and variations in total amount, 540
pressure, high; effect of arteriosclerosis and benign and malignant hypertension on area of histamine flares, 865
pressure, high; heredity in arteriolar (essential) hypertension; clinical study of 1,524 members of 277 families, 792
pressure, high; malignant hypertension; histologic changes in kidneys, 832
pressure, high; relation of plasma cholesterol to obesity and to some complicating degenerative diseases (diabetes mellitus, essential hypertension, osteo-arthritis and arteriosclerosis), 423
pressure; spinal fluid pressure and venous pressure in cardiac failure and effect of spinal drainage in treatment of cardiac decompensation, 782
sugar; effect of toxemia on tolerance for dextrose and on action of insulin, 689
sugar tolerance and insulin in thin people, 153
vessels, arteritis of temporal vessels; previously undescribed form, 400
Blotner, H.: Insulin and sugar tolerance in thin people, 153

Book Reviews:

Angina de pecho; G. N. Martinez, 162
Arritmias; A. Battro, 632
Arteriosclerosis; edited by E. J. Cowdry, 162
Biochemistry of Medicine; A. T. Cameron, and C. R. Gilmour, 807
Chronic Indigestion; T. C. Hunt, 323
Chronic Nephritis and Lead Poisoning; L. J. J. Nye, 478
Congrès français de médecine, Twelfth Session, 1932, 631
Diabetes Mellitus; I. M. Rabinowitch, 806
Exploration fonctionnelle de la rate; E. Benhamou, 160
Fonctions gastro-duodénales; J. Dimitresco-Popovici, 163
Food and Principles of Dietetics; R. Hutchinson and V. H. Mottram, 163
Food, Nutrition and Health; E. V. McCollum and J. E. Becker, 322
Fortschritte der Serologie; H. Schmidt, 163

BOOK REVIEWS—Continued
Función hemo-respiratoria en los "Cardiacos Negro de Ayerza"; I. Berconsky, 164
Grandes hémorragies gastro-duodénales. Etude Médico-Chirurgicale; L. Tixier and C. Clavel, 321
Handbook of Chemotherapy: Part 1. Metal-Free Organic Compounds; V. Fischl and H. Schlossberger, 480
Handbuch der allgemeinen Hämatologie; H. Hirschfeld and A. Hittmair, 804
Hémorrhoides; J. Rachet, 808
History of Urology; Prepared under the auspices of the American Urological Association, 161
Klassifikation der Schizomyceten (Bakterien): Versuch einer wissenschaftlichen Klassifikation der Bakterien auf botanischer Grundlage; E. Pribram, 479
Luft- und Fettembolie; S. Hoffheinz, 323
Metabolic Diseases and Their Treatment; E. Grafe, 631
Modern Aspects of Gastro-Enterology; M. A. Arafa, 160
Modern Treatment of Syphilis; J. E. Moore, 632
Pediatrics; H. D. Chapin and L. T. Royster, 805
Peptic Ulcer; J. Buckstein, 161
Principles of Human Physiology; E. H. Starling, 632
Rythmes et la vie; Laignel-Lavastine, A. M. Chanoz, J. Monchanin, G. Richard, J. Guitton, F. Mentré, H. Duprat, H. Cardot and R. Biot, 807
Sinus carotidien et la zone homologue cardio-aortique; C. Heymans, J. J. Bouckaert and P. Regniers, 162
Strophanthin Therapy: Comments on Quantitative Administration of Digitalis According to Pharmacologic Principles; A. Fraenkel, in collaboration with R. Thauer, 321
Surgery of Stomach and Duodenum; J. S. Horsley, 323
Technic of Local Anesthesia; A. E. Hertzler, 321
Text-Book of Medicine: by 141 American authors. Edited by R. L. Cecil and F. Kennedy, 478
Therapeutic Agents of Quinoline Group; W. F. von Oettingen, 163
Traité de physiologie normale et pathologique: Tome I. Physiologie générale; G. H. Roger and L. Binet, 480
Tratado de la diabetes; P. Escudero, 479
Tuberculin: Its Vindication by Technique with Special Reference to Tuberculous Disease of the Eye; W. C. Wilkinson, 159
Verhandlungen der deutschen Gesellschaft für Kreislaufforschung; B. Kisch, 322

Boothby, W. M.: Myasthenia gravis; effect of treatment with glycine and ephedrine, 39
Brown, G. E.: Arteritis of temporal vessels; previously undescribed form, 400
Bruger, M.: Relation of plasma cholesterol to obesity and to some complicating degenerative diseases (diabetes mellitus, essential hypertension, osteo-arthritis and arteriosclerosis), 423

Cain, E. F.: Malignant hypertension; histologic changes in kidneys, 832
Calcium deposition in diabetes mellitus, abnormalities of, 46
Calhoun, J. A.: Congestive heart failure; Cheyne-Stokes respiration as cause of paroxysmal dyspnea at onset of sleep, 891
Congestive heart failure; clinical types of nocturnal dyspnea, 561
Congestive heart failure; observations concerning mechanism of cardiac asthma, 911
Congestive heart failure; reflex stimulation of respiration as cause of evening dyspnea, 724
Camp, J. D.: Chronic idiopathic steatorrhea; roentgenologic observations, 615
Cancer: See under names of organs and regions
Cerebrospinal Fluid pressure and venous pressure in cardiac failure and effect of spinal drainage in treatment of cardiac decompensation, 782
Cheyne-Stokes' Respiration: See Respiration
Christian-Schüller Syndrome: See Schüller-Christian Syndrome
Chyluria: See Urine, chyle
Colitis, relapses in chronic ulcerative colitis, causes and prevention, 131
Connor, C. L.: Generalized thrombo-angiitis obliterans; report of case with involvement of retinal vessels and suprarenal infarction, 410
Cookson, H. A.: True nonparasitic chyluria associated with menstruation; report of case, 878
Cowgill, G. R.: Physiology of vitamins; effect of lack of vitamin B complex on secretion of gastric juice in dogs with gastric pouches, 58
Cowie, D. M.: Lipoids and lipoid diseases; lipoid content of tissues in Schüller-Christian's disease (xanthomatosis) and review of literature on lipoid content of human tissues, 391
Craig, H. R.: Etiology and symptoms of neurocirculatory asthenia; analysis of 100 cases with comments on prognosis and treatment, 633
Creatine, differences in creatine concentration of left and right ventricular cardiac muscles, 574
Cretinism: See also Myxedema
incidence of, 324

Dextrose, effect of toxemia on tolerance for dextrose and on action of insulin, 689
Diabetes Mellitus: See also Insulin
abnormalities of calcium deposition in, 46
relation of plasma cholesterol to obesity and to some complicating degenerative diseases (diabetes mellitus, essential hypertension, osteo-arthritis and arteriosclerosis), 423
Dieckmann, W. J.: Blood in normal pregnancy; blood and plasma volumes, 71
Blood in normal pregnancy; conductivity, total base, chloride and acid-base equilibrium, 527
Blood in normal pregnancy; hemoglobin and cell volume coefficients; erythrocyte volume, hemoglobin content and concentration; color, volume and saturation indexes, 345
Blood in normal pregnancy; hemoglobin, hematocrit and erythrocyte determinations and total amount of variations of each, 188
Blood in normal pregnancy; percentages and grams per kilogram of serum protein and fibrin and variations in total amount of each, 353
Blood in normal pregnancy; plasma cholesterol in milligrams per hundred cubic centimeters, grams per kilogram and variations in total amount, 540
Digestive tract, changes of digestive tract in uremia; pathologic anatomic study, 851
Duodenum Ulcer: See Peptic Ulcer
Dyspnea, congestive heart failure; Cheyne-Stokes respiration as cause of paroxysmal dyspnea at onset of sleep, 891
congestive heart failure; clinical types of nocturnal dyspnea, 561
congestive heart failure; reflex stimulation of respiration as cause of evening dyspnea, 724
Dystrophy, muscular, and atrophy; clinical and biochemical results following oral administration of amino-acids, 435

Eaton, F. B.: Experimental postoperative edema, 649
Edema, experimental, postoperative, 649
Ehrlich, J. C.: Periosteal ossification in myelogenous leukemia; report of case associated with acute rheumatic fever, 938

Endocarditis, acute Streptococcus viridans endocarditis; report of 4 cases with autopsy observations in 2, 508
acute, with Salmonella suipestifer bacteremia, 699
Enzymes, determination of, on autopsy specimens from cases of pernicious anemia and pellegra, 675
Eppinger, E. C.: Angina pectoris; clinical considerations with reference to prognosis, 120
Ernstene, A. C.: Effect of arteriosclerosis and benign and malignant hypertension on area of histamine flares, 865
Erythrocytes, blood in normal pregnancy; hemoglobin and cell volume coefficients; erythrocyte volume, hemoglobin content and concentration; color, volume and saturation indexes, 345
blood in normal pregnancy; hemoglobin, hematocrit and erythrocyte determinations and total amount of variations of each, 188
Exercise, metabolic exercise tolerance test for patients with cardiac disease; feasible method for using excess oxygen consumption and recovery time of exercise as criteria of cardiac status, 710
metabolic exercise tolerance test; simplified method, 706

Feces, fat in; chronic idiopathic steatorrhea; roentgenologic observations, 615
Feldman, W. H.: Comparison of development of specific nodule of silicosis and of tuberculosis, 367
Ferrigan, J. P., Jr.: Cardiac output: its related functions in case of coarctation of aorta, 35
Finland, M.: Infections with pneumococcus type III and type VIII; characterization of pneumonia caused by pneumococcus type III and that associated with biologically closely related organism, pneumococcus type VIII, 481
Forer, S.: Periosteal ossification in myelogenous leukemia; report of case associated with acute rheumatic fever, 938
Forkner, C. E.: Clinical and pathologic differentiation of acute leukemias with reference to acute monocytic leukemia, 1
Fouts, P. J.: Gastro-intestinal studies; determinations of enzymes on autopsy specimens from cases of pernicious anemia and pellagra, 675

Gastric Ulcer: See Peptic Ulcer
Gastro-Intestinal Tract; determinations of enzymes on autopsy specimens from cases of pernicious anemia and pellagra, 675
German Society for Circulatory Research, meeting, 164
Gilman, A.: Physiology of vitamins; effect of lack of vitamin B complex on secretion of gastric juice in dogs with gastric pouches, 58
Goldbloom, A. A.: Acute Streptococcus viridans endocarditis; report of 4 cases with autopsy observations in 2, 508
Goldhamer, S. M.: Liver extract therapy in cirrhosis of liver; relation of liver dysfunction to nonstorage of "anti-anemic" substance in producing blood picture resembling pernicious anemia in patient secreting free hydrochloric acid, 54
Goodall, H. W.: Thoracic stomach; report of 5 cases, 594
Gouley, B. A.: Salmonella suipestifer bacteremia with acute endocarditis, 699
Graeser, J. B.: Physical signs and roentgenographic findings in lobar pneumonia in adults, 249
Grollman, A.: Cardiac output; its related functions in a case of coarctation of aorta, 35

Hallman, F. A.: Rheumatoid (atrophic) arthritis; bacteriologic cultures of synovial fluid and of tissues, 87
Harrison, T. R.: Congestive heart failure; Cheyne-Stokes respiration as cause of paroxysmal dyspnea at onset of sleep, 891
Congestive heart failure; clinical types of nocturnal dyspnea, 561
Congestive heart failure; observations concerning mechanism of cardiac asthma, 911
Congestive heart failure; reflex stimulation of respiration as cause of evening dyspnea, 724
Harrison, W. G., Jr.: Cerebrospinal fluid pressure and venous pressure in cardiac failure and effect of spinal drainage in treatment of cardiac decompensation, 782
Congestive heart failure; Cheyne-Stokes respiration as cause of paroxysmal dyspnea at onset of sleep, 891
Congestive heart failure; clinical types of nocturnal dyspnea, 561
Congestive heart failure; observations concerning mechanism of cardiac asthma, 911
Congestive heart failure; reflex stimulation of respiration as cause of evening dyspnea, 724
Heart: See also Endocarditis
block; nature and significance of heart sounds and of apex impulses in bundle branch block, 741
cardiac output; its related functions in case of coarctation of aorta, 35
difference in creatine concentration of left and right ventricular cardiac muscles, 574
disease, metabolic exercise tolerance test for patients with cardiac disease; feasible method for using excess oxygen consumption and recovery time of exercise as criteria of cardiac status, 710
failure; cerebrospinal fluid pressure and venous pressure in cardiac failure and effect of spinal drainage in treatment of cardiac decompensation, 782
failure, congestive; Cheyne-Stokes respiration as cause of paroxysmal dyspnea at onset of sleep, 891
failure, congestive, clinical types of nocturnal dyspnea, 561
failure, congestive, observations concerning mechanism of cardiac asthma, 911
failure, congestive; reflex stimulation of respiration as cause of evening dyspnea, 724
in myxedema, 165
Heinz, T. E.: Mechanism of pain in gastric and duodenal ulcers; further observations, 269
Held, I. W.: Acute Streptococcus viridans endocarditis; report of 4 cases with autopsy observations in 2, 508
Helmer, O. M.: Gastro-intestinal studies; determinations of enzymes on autopsy specimens from cases of pernicious anemia and pellagra, 675
Hemoglobin, blood in normal pregnancy; hemoglobin and cell volume coefficients; erythrocyte volume, hemoglobin content and concentration; color, volume and saturation indexes, 345
blood in normal pregnancy; hemoglobin, hematocrit and erythrocyte determinations and total amount of variations of each, 188
Henner, R.: Metabolic exercise tolerance test; simplified method, 706
Histamine, effect of arteriosclerosis and benign and malignant hypertension on area of histamine flares, 865
Horton, B. T.: Arteritis of temporal vessels; previously undescribed form, 400
Hoyt, L. H.: Thoracic stomach; report of 5 cases, 594
Hurxthal, L. M.: Blood cholesterol and hypometabolism; suprarenal and pituitary deficiency, obesity and miscellaneous conditions, 825
Blood cholesterol and thyroid disease; myxedema and hypercholesteremia, 762
Hypercholesteremia: See Blood, cholesterol
Hypertension: See Blood pressure, high

Insulin: See also Diabetes Mellitus
and sugar tolerance in thin people, 153
effect of toxemia on tolerance for dextrose and on action of insulin, 689
Iron, constancy in blood plasma and in urine in health and in anemia, 551
Irwin, R. L.: Relationship between anatomic changes in knee joint with advancing age and degenerative arthritis, 325
Ischemia, factors involved in production of skeletal muscle pain, 814
Israel, S. L.: Salmonella suipestifer bacteremia with acute endocarditis, 699

Jaffé, R. H.: Changes in digestive tract in uremia; pathologic anatomic study, 851
Jaundice, residual hepatic damage in catarrhal jaundice as determined by bilirubin excretion test, 809
Jones, C. M.: Experimental postoperative edema, 649

Katz, L. N.: Factors involved in production of skeletal muscle pain, 814
Metabolic exercise tolerance test for patients with cardiac disease; feasible method for using excess oxygen consumption and recovery time of exercise as criteria of cardiac status, 710
Metabolic exercise tolerance test; simplified method, 706
Kay, H. D.: Osteitis deformans, 208
Keefer, C. S.: Relationship between anatomic changes in knee joint with advancing age and degenerative arthritis, 325
Kidneys, histologic changes in, in malignant hypertension, 832
King, C. E.: Congestive heart failure; Cheyne-Stokes respiration as cause of paroxysmal dyspnea at onset of sleep, 891
Knee, relationship between anatomic changes in knee joint with advancing age and degenerative arthritis, 325

Laing, D. R.: Changes of digestive tract in uremia; pathologic anatomic study, 851
Lemon, W. S.: Comparison of development of specific nodule of silicosis and of tuberculosis, 367
Leukemia, acute clinical and pathologic differentiation of, with reference to acute monocytic leukemia, 1
periosteal ossification in myelogenous leukemia; report of case associated with acute rheumatic fever, 938
Levine, S. A.: Angina pectoris; clinical considerations with reference to prognosis, 120
Lewis, J. K.: Nature and significance of heart sounds and of apex impulses in bundle branch block, 741
Lichtman, S. S.: Origin and significance of tyrosinuria in diseases of liver, 680
Lichty, D. E.: Lipoids and lipoid diseases; xanthomatosis (Schüller-Christian's syndrome), 379
Linegar, C. R.: Difference in creatine concentration of left and right ventricular cardiac muscles, 574
Lipoid and lipoid diseases; lipoid content of tissues in Schüller-Christian's disease (xanthomatosis) and review of literature on lipoid content of human tissues, 391
and lipoid diseases; xanthomatosis (Schüller-Christian's syndrome), 379
Liver, cirrhosis, liver extract therapy in; relation of liver dysfunction to nonstorage of "anti-anemic" substance in producing blood picture resembling pernicious anemia in patient secreting free hydrochloric acid, 54
disease, origin and significance of tyrosinuria in, 680
residual hepatic damage in catarrhal jaundice as determined by bilirubin excretion test, 809
LoBello, L. C.: Effect of toxemia on tolerance for dextrose and on action of insulin, 689

Magath, T. R.: Arteritis of temporal vessels; previously undescribed form, 400
Magee, M. C.: Lipoids and lipoid diseases; lipoid content of tissues in Schüller-Christian's disease (xanthomatosis) and review of literature on lipoid content of human tissues, 391
Malaria therapy, plasmochin, plasmochin with quinine salts and atabrine in, 309
Marble, A.: Abnormalities of calcium deposition in diabetes mellitus, 46
Markle, P.: Factors involved in production of skeletal muscle pain, 814
Metabolic exercise tolerance test; simplified method, 706
Marlow, A.: Constancy of iron in blood plasma and urine in health and in anemia, 551
Marsh, J. P.: Congestive heart failure; reflex stimulation of respiration as cause of evening dyspnea, 724
Menstruation, true nonparasitic chyluria associated with menstruation; report of case, 878
Mercuric chloride, acid-base balance in pathologic condition; serum electrolyte changes in acute mercuric chloride poisoning, 885
Metabolism, blood cholesterol and hypometabolism; suprarenal and pituitary deficiency, obesity and miscellaneous conditions, 825
metabolic exercise tolerance test for patients with cardiac disease; feasible method for using excess oxygen consumption and recovery time of exercise as criteria of cardiac status, 710
metabolic exercise tolerance test; simplified method, 706
Muntwyler, E.: Acid-base balance in pathologic conditions; serum electrolyte changes in acute mercuric chloride poisoning, 885
Muscle, difference in creatine concentration of left and right ventricular cardiac muscles, 574
Dystrophy: See under Dystrophy
factors involved in production of skeletal muscle pain, 814
Myasthenia gravis, effect of treatment with glycine and ephedrine, 39
Myers, V. C.: Difference in creatine concentration of left and right ventricular cardiac muscles, 574
Myers, W. K.: Relationship between anatomic changes in knee joint with advancing age and degenerative arthritis, 325
Myxedema, blood cholesterol and thyroid disease; myxedema and hypercholesteremia, 762
heart in, 165

Obesity, blood cholesterol and hypometabolism; suprarenal and pituitary deficiency, obesity and miscellaneous conditions, 825
relation of plasma cholesterol to obesity and to some complicating degenerative diseases (diabetes mellitus, essential hypertension, osteo-arthritis and arteriosclerosis), 423
Ohler, W. R.: Heart in myxedema, 165
Osteoarthritis, relation of plasma cholesterol to obesity and to some complicating degenerative diseases (diabetes mellitus, essential hypertension, osteo-arthritis and arteriosclerosis), 423
Osteitis deformans, 208

Palmer, W. L.: Mechanism of pain in gastric and duodenal ulcers; further observations, 269
Parker, F., Jr.: Relationship between anatomic changes in knee joint with advancing age and degenerative arthritis, 325
Paulson, M.: Residual hepatic damage in catarrhal jaundice as determined by bilirubin excretion test, 809
Pellagra, gastro-intestinal studies; determinations of enzymes on autopsy specimens from cases of pernicious anemia and pellagra, 675

Peptic Ulcer, clinical consideration of etiology, 97
mechanism of pain in gastric and duodenal ulcers; further observations, 269
Periosteum, periosteal ossification in myelogenous leukemia; report of case associated with acute rheumatic fever, 938
Perlow, S.: Factors involved in production of skeletal muscle pain, 814
Pituitary, blood cholesterol and hypometabolism; suprarenal and pituitary deficiency, obesity and miscellaneous conditions, 825
Plasmochin: See Malaria therapy
Plaut, J. L.: Metabolic exercise tolerance test for patients with cardiac disease; feasible method for using excess oxygen consumption and recovery time of exercise as criteria of cardiac status, 710
Pneumococci, infections with pneumococcus type III and type VIII; characterization of pneumonia caused by pneumococcus type III and that associated with biologically closely related organism, pneumococcus type VIII, 481
Pneumonia, characterization of, caused by pneumococcus type III and that associated with a biologically closely related organism, pneumococcus type VIII, 481
lobar, physical signs and roentgenographic findings in adults, 249
Poindexter, C. A.: Relation of plasma cholesterol to obesity and to some complicating degenerative diseases (diabetes mellitus, essential hypertension, osteo-arthritis and arteriosclerosis), 423
Pomerene, E.: Acid-base balance in pathologic conditions; serum electrolyte changes in acute mercuric chloride poisoning, 885
Pregnancy, normal, blood in; blood and plasma volumes, 71
normal, blood in; conductivity, total base, chloride and acid-base equilibrium, 527
normal, blood in; hemoglobin and cell volume coefficients; erythrocyte volume, hemoglobin content and concentration; color, volume and saturation indexes, 345
normal, blood in; hemoglobin, hematocrit and erythrocyte determinations and total amount of variations of each, 188
normal, blood in; percentages and grams per kilogram of serum protein and fibrin and variations in total amount of each, 353
normal, blood in; plasma cholesterol, in milligrams per hundred cubic centimeters, grams per kilogram and variations in total amount, 540
Prinzmetal, M.: Generalized thrombo-angiitis obliterans; report of case with involvement of retinal vessels and suprarenal infarction, 410
Prize, Edward M. Gibbs Memorial Prize, 803
Puilar, T. H.: True nonparasitic chyluria associated with menstruation; report of case, 878

Respiration, congestive heart failure; Cheyne-Stokes respiration as cause of paroxysmal dyspnea at onset of sleep, 891
congestive heart failure; reflex stimulation of respiration as cause of evening dyspnea, 724
Retina, generalized thrombo-angiitis obliterans; report of case with involvement of retinal vessels and suprarenal infarction, 410
Rheumatic Fever, bacteriologic study of throats in rheumatic and nonrheumatic fever with reference to hemolytic streptococci, 453
periosteal ossification in myelogenous leukemia; report of case associated with acute rheumatic fever, 938
Riddoch, G.: Osteitis deformans, 208
Rivers, A. B.: Clinical consideration of etiology of peptic ulcer, 97
Robertson, O. H.: Physical signs and roentgenographic findings in lobar pneumonia in adults, 249
Root, H. F.: Abnormalities of calcium deposition in diabetes mellitus, 46
Russell, P. F.: Plasmochin, plasmochin with quinine salts and atabrine in malaria therapy, 309

Sager, R. V.: Coronary thrombosis; perforation of infarcted interventricular septum, 140
Salmonella suipestifer bacteremia with acute endocarditis, 699
Schüller-Christian Syndrome, lipoids and lipoid diseases; lipoid content of tissues in Schüller-Christian's disease (xanthomatosis) and review of literature on lipoid content of human tissues, 391
lipoids and lipoid diseases; xanthomatosis, 379
Schutz, W. J.: Metabolic exercise tolerance test for patients with cardiac disease; feasible method for using excess oxygen consumption and recovery time of exercise as criteria of cardiac status, 710
Seecof, D. P.: Difference in creatine concentration of left and right ventricular cardiac muscles, 574
Silicosis, comparison of development of specific nodule of silicosis and of tuberculosis, 367
Simpson, S. L.: Osteitis deformans, 208
Snell, A. M.: Chronic idiopathic steatorrhea: roentgenologic observations, 615
Snyder, M.: Effect of arteriosclerosis and benign and malignant hypertension on area of histamine flares, 865
Soffer, L. J.: Residual hepatic damage in catarrhal jaundice as determined by bilirubin excretion test, 809
Soskin, S.: Metabolic exercise tolerance test for patients with cardiac disease; feasible method for using excess oxygen consumption and recovery time of exercise as criteria of cardiac status, 710
Metabolic exercise tolerance test; simplified method, 706
Steatorrhea: See Feces, fat in
Stomach: See also Gastro-Intestinal Tract
secretion; physiology of vitamins; effect of lack of vitamin B complex on secretion of gastric juice in dogs with gastric pouches, 58
thoracic, report of 5 cases, 594
Ulcer: See Peptic Ulcer
Stool: See Feces
Streptococci, hemolytic, bacteriologic study of throats in rheumatic fever and nonrheumatic fever with reference to, 453
viridans, acute Streptococcus viridans endocarditis; report of 4 cases with autopsy observations in 2, 508
Styron, N. C.: Bacteriologic study of throats in rheumatic and nonrheumatic fever with reference to hemolytic streptococci, 453
Sugar in Blood: See Blood
Suprarenals, blood cholesterol and hypometabolism; suprarenal and pituitary deficiency, obesity and miscellaneous conditions, 825
generalized thrombo-angiitis obliterans; report of case with involvement of retinal vessels and suprarenal infarction, 410
Sutliff, W. D.: Infections with pneumococcus type III and type VIII; characterization of pneumonia caused by pneumococcus type III and that associated with biologically closely related organism, pneumococcus type VIII, 481
Sweeney, J. S.: Effect of toxemia on tolerance for dextrose and on action of insulin, 689

Taylor, F. H. L.: Constancy of iron in blood plasma and urine in health and in anemia, 551
Temporal vessels, arteritis of; previously undescribed form, 400
Thrombo-angiitis obliterans, generalized: report of case with involvement of retinal vessels and suprarenal infarction, 410
Thrombosis, coronary perforation of infarcted interventicular septum, 140

Thyroid disease and blood cholesterol; myxedema and hypercholesteremia, 762
Toxemia, effect on tolerance for dextrose and on action of insulin, 689
Tripoli, C. J.: Muscular dystrophy and atrophy; clinical and biochemical results following oral administration of amino-acids, 435
Tuberculosis, comparison of development of specific nodule of silicosis and of tuberculosis, 367
Tyrosinuria: See Urine, tyrosine

Uremia, changes of digestive tract in uremia, pathologic anatomic study, 851
Urine, chyle; true nonparasitic chyluria associated with menstruation; report of case, 878
constancy of iron in blood plasma and urine in health and in anemia, 551
residual hepatic damage in catarrhal jaundice as determined by bilirubin excretion test, 809
tyrosine, origin and significance in disease of liver, 680

Venous Pressure: See under Blood
Vitamins, physiology; effect of lack of vitamin B complex on secretion of gastric juice in dogs with gastric pouches, 58

Way, C. T.: Acid-base balance in pathologic conditions; serum electrolyte changes in acute mercuric chloride poisoning, 885
Wegner, C. R.: Blood in normal pregnancy; blood and plasma volumes, 71
Blood in normal pregnancy: conductivity, total base, chloride and acid-base equilibrium, 527
Wegner, C. R.—Continued
Blood in normal pregnancy; hemoglobin and cell volume coefficients; erythrocyte volume, hemoglobin content and concentration; color, volume and saturation indexes, 345
Blood in normal pregnancy; hemoglobin, hematocrit and erythrocyte determinations and total amount of variations of each, 188
Blood in normal pregnancy; percentages and grams per kilogram of serum protein and fibrin and variations in total amount of each, 353
Blood in normal pregnancy; plasma cholesterol in milligrams per hundred cubic centimeters, grams per kilogram and variations in total amount, 540
Weinstein, I.: Bacteriologic study of throats in rheumatic and nonrheumatic fever with reference to hemolytic streptococci, 453
White, J. C.: Experimental postoperative edema, 649
White, P.: Abnormalities of calcium deposition in diabetes mellitus, 46
White, P. D.: Etiology and symptoms of neurocirculatory asthenia; analysis of 100 cases with comments on prognosis and treatment, 633
Wu, C.: Physical signs and roentgenographic findings in lobar pneumonia in adults, 249

Xanthomatosis: See Schüller-Christian Syndrome

Zerfas, L. G.: Gastro-intestinal studies; determinations of enzymes and autopsy specimens from cases of pernicious anemia and pellagra, 675

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CONTENTS

PAGE

Residual Hepatic Damage in Catarrhal Jaundice as Determined by the Bilirubin Excretion Test. Louis J. Soffer, M.D., and Moses Paulson, M.D., Baltimore..... 809

Factors Involved in the Production of Skeletal Muscle Pain. S. Perlow, M.D.; P. Marble, M.D., and L. N. Katz, M.D., Chicago..... 814

Blood Cholesterol and Hypometabolism: Suprarenal and Pituitary Deficiency, Obesity and Miscellaneous Conditions. Lewis M. Hurxthal, M.D., Boston..... 825

Malignant Hypertension: The Histologic Changes in the Kidneys. Edmund F. Cain, M.D., Rochester, Minn..... 832

Changes of the Digestive Tract in Uremia: A Pathologic Anatomic Study. R. H. Jaffé, M.D., and D. R. Laing, M.D., Chicago..... 851

Effect of Arteriosclerosis and Benign and Malignant Hypertension on Area of Histamine Flares. A. Carlton Ernstene, M.D., and Maurice Snyder, M.D., Cleveland. 865

True Nonparasitic Chyluria Associated with Menstruation: Report of a Case. H. A. Cookson, M.B., F.R.C.S., E., D.P.H., and T. H. Pullar, M.B., Ch.B., M.R.C.P. (London), Sunderland, England..... 878

The Acid-Base Balance in Pathologic Conditions: III. Serum Electrolyte Changes in Acute Mercuric Chloride Poisoning. Edward Muntwyler, Ph.D.; Charles T. Way, M.D., and Elizabeth Pomerene, Ph.D., Cleveland. 885

Congestive Heart Failure:

XX. Cheyne-Stokes Respiration as the Cause of Paroxysmal Dyspnea at the Onset of Sleep. T. R. Harrison, M.D.; C. E. King, M.D.; J. A. Calhoun, M.D., and W. G. Harrison Jr., M.D., Nashville, Tenn..... 891

XXI. Observations Concerning the Mechanism of Cardiac Asthma. T. R. Harrison, M.D.; J. A. Calhoun, M.D., and W. G. Harrison Jr., M.D., Nashville, Tenn..... 911

Periosteal Ossification in Myelogenous Leukemia: Report of a Case Associated with Acute Rheumatic Fever. Joseph C. Ehrlich, M.D., and Samuel Forer, M.D., New York..... 938

General Index..... 953